Review Article

Indian J Med Res 139, June 2014, pp 805-813

Food allergy: Diagnosis, management & emerging therapies

Rachel Glick Robison[1, 2]

[1]*Division of Allergy & Immunology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois &* [2]*Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA*

Received May 1, 2013

IgE-mediated food allergy is an important health concern with increasing prevalence worldwide. Manifestations of IgE-mediated food allergy include urticaria, angioedema, pruritus, difficulty in breathing, laryngeal oedema, vomiting, diarrhoea and/or hypotension within minutes to two hours of the offending food's ingestion. Diagnosis requires both a careful history and supportive testing with laboratory studies and possibly oral food challenges. Current treatment of food allergy focuses on avoidance of the allergen and prompt emergency management of reactions. Epinephrine autoinjectors are provided to patients for the treatment of severe reactions. More research is needed to determine the optimal timing with which to introduce common allergens into a child's diet to possibly prevent the development of food allergy. Novel therapies are under investigation given the difficulty of allergen avoidance and the potentially fatal nature of reactions. Both allergen specific therapies such as oral, sublingual and epicutaneous immunotherapy and allergen non-specific therapies such the Chinese herbal formula FAHF-2 and omalizumab show promise though more data on efficacy and long-term safety are needed before these therapies become mainstream.

Key words Anaphylaxis - avoidance - diagnosis - food allergy - skin prick test - testing - treatment

Introduction

A food allergy is an "adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food[1]". Food allergy is an important health concern as it affects both children and adults with increasing prevalence worldwide. Estimates of food allergy's true prevalence have been difficult to establish as most studies are based on self-report and not on established diagnosis via skin or blood testing and food challenge. In a meta-analysis by Rona *et al*[2], self-reported prevalence of food allergy varied from 1.2 to 17 per cent for milk, 0.2 to 7 per cent for egg, 0 to 2 per cent for peanuts and fish, 0 to 10 per cent for shellfish, and 3 to 35 per cent for any food. Prevalence in the United States was recently estimated at approximately 2.5 per cent for peanut, milk, egg, and/or shrimp when taking into account food specific IgE levels finding an increased association with childhood age, male sex, and non-Hispanic black race/ethnicity[3]. Along similar lines, a recent Australian study of challenge proven food allergy in 12 month old children found a prevalence of 3 per cent for peanut, 8.9 per cent for egg and 0.8 per cent for sesame allergy[4]. In Asia, prevalence figures remain similar to those in the western world, despite

the perception that allergy is less prevalent[5]. Given this continued increase in prevalence, the potentially fatal outcome of food-induced anaphylaxis and the lack of standardized therapy, food allergy demands further attention and study.

Though many adverse reactions to food exist, this review focuses solely on immunoglobulin E (IgE) mediated food allergy. Hallmark manifestations of IgE-mediated food allergy include urticaria, angioedema, pruritus, difficulty in breathing, laryngeal oedema, vomiting, diarrhoea and/or hypotension. While cutaneous symptoms are the most common sign of reactions, up to 20 per cent of cases may not present with skin findings, especially as the patient ages, and, therefore, a lack of rash does not rule out anaphylaxis[6,7]. These symptoms typically develop within minutes to two hours of ingestion of the food allergen and are reproducible upon each ingestion. The constellation of symptoms involving two or more organ symptoms leading to anaphylaxis can be fatal if not treated promptly. The goal of this review is to highlight the diagnosis, current management and evolving therapeutics for IgE-mediated food allergy.

World experience

Though food allergy has been noted in the urbanized western world for sometime, it is becoming increasingly prevalent throughout the world. However, a few studies are published estimating prevalence data and there appears to be a difference in which allergens are more prevalent in each country.

In the western world, cow's milk and egg are the most common allergens in infants and young children[8]. Typically these allergies are outgrown by late childhood[9,10]. Similar to the United States (US) and the United Kingdom (UK), in most of Asia egg and milk remain the most common allergens in young children[5]. However, in older children and adults, shellfish is the most common food allergen[11]. Yet in Korea, wheat and buckwheat are the most common causes of food-induced anaphylaxis[12]. Allergens that may seem atypical in some areas of the world are widespread in certain countries like Singapore where the delicacy bird's nest soup is the most common food allergen[13]. These differences likely are reflective of differences in allergen exposure, handling and processing, though differences may also be affected by environmental levels of exposure or genetic differences[14].

Diagnosis

A detailed and careful patient history is of utmost importance in the diagnosis of food allergy. This history should include manifestations, timing, and reproducibility of all past reactions. A focused physical examination should be performed though is often unrevealing outside of reactions, asides from manifestations of potential co-morbid atopic conditions such as rhinitis and atopic dermatitis. All reports of food allergy should be confirmed as recommended by the National Institute of Allergy and Infectious Diseases (NIAID) Expert Panel Report published in 2010[1] as multiple studies demonstrate that much of presumed food allergy is in error[15].

Physicians have several tests available at hand for the diagnosis of food allergy. Should the history be suggestive of a typical food reaction, confirmation with *in vivo*/*in vitro* testing is recommended. Both skin prick testing (SPT) and *in vitro* serum IgE testing are used routinely in practice to confirm a food allergy once reported. Unproven tests for food allergy include serum IgG4 testing which can be performed to many foods, however, its presence is not known to play a role in the immunology of food allergy[16].

SPT: SPT involves the introduction of the food protein in the superficial layer of the skin and requires the patient to be free of antihistamines. The testing is inexpensive and results are immediately available while the patient is in the office. Intradermal testing is not advised for testing of food allergy. Positive testing alone by skin or blood testing, however, does not confirm food allergy as neither mode of testing has a high predictive value. Though skin testing is quite sensitive, it is not very specific[17]. A negative test mostly confirms a lack of IgE-mediated allergy if performed correctly with histamine and saline control tests[18]. Presence of food specific IgE without a suspicious reaction indicates sensitization, but is not always representative of a true allergy. However, larger wheal size on skin testing has been correlated with an increased likelihood of clinical allergy upon open food challenge[19].

Serum specific-IgE testing: *In vitro* serum IgE testing quantifies the amount of IgE to the food-specific protein via an enzymatic assay. Serum testing is readily available and does not require that the patient be free of antihistamines; however, there is a higher cost and the need to obtain a blood sample. Several commercial assays are available however, significant differences in the measured IgE levels have been found between

assays using identical serum samples[20]. Therefore, the assays are not interchangeable. Analogous to the trends noted with skin prick testing, largely positive food-specific IgE levels have been found to correlate with a likelihood of clinical reaction[18, 21]. Specialists have data at hand with levels that are >95 per cent predictive of reaction among children for common allergens such as egg, peanut and milk[21, 22].

In an effort to distinguish true allergy from sensitization new testing, termed component-resolved diagnostics (CRD), has been established. This testing targets individual, pure allergen proteins[23]. Thus far, component testing has been noted to be particularly helpful in differentiating between asymptomatic sensitization and peanut allergy. Positivity to storage proteins rAra h 1, rAra h 2, and rAra h 3 are more associated with immediate, clinical reactions to peanut, whereas positivity to rAra h 8 (a Bet v 1, or birch pollen, homologue) is more associated with a milder birch pollen related oral allergy syndrome[24]. However, the clinical relevance is not yet well established for other food proteins and some studies show increase specificity with testing, but decreased sensitivity when compared to traditional testing[20]. CRD testing will likely become more prevalent once its full utility is understood.

Oral food challenges: A food allergy diagnosis is supported when reaction symptoms and testing correlate. To confirm the diagnosis of food allergy in some instances or to determine if tolerance to an allergen has been achieved (*i.e*. a food allergy outgrown), an oral food challenge (OFC) may be performed.In an OFC, the offending food allergen is given to the patient in escalating doses either in an open or blinded fashion. Typically, the challenge occurs in the clinic setting under direct observation so that possible reactions may be treated promptly. For the gold standard diagnosis of food allergy, the challenge should be performed in a double-blind placebo controlled fashion though this is costly and often difficult in practice. Therefore, many allergy specialists choose to employ open feeding challenges.In a survey of American Academy of Asthma, Allergy& Immunology members practicing in the US, 85.5 per cent of allergists reported that they perform challenges, however, a very small number of allergists (5.6%) performed more than 10 OFCs per month, while 70 per cent performed only 1 to 5 OFCs per month[25]. The decision to have a patient undergo an OFC may be dependent on several factors including severity of past reactions, patient age, disease comorbidities and patient anxiety[26]. These OFCs have been determined to be safe when performed on selected patients in the hands of experienced personnel and biphasic, or delayed/late phase reactions, have been noted to be rare in these instances[27].

Management

Avoidance: Once the diagnosis of a food allergy is established the patient should be instructed to completely avoid the allergen. Unfortunately, avoidance is easier said than done and as hidden allergens pose a possible fatal risk, the patient should be provided with an emergency plan for medications and actions to be given should accidental ingestion occur. In a study of peanut allergic children in Quebec, an annual incidence rate of accidental exposure was found to be 14.3 per cent with the majority of ingestions occurring at the patient's home or at the home of a friend or relative[28]. This was followed by a nationwide survey in Canada finding an annual peanut accidental ingestion incidence of 12.5 per cent when excluding recently diagnosed individuals[29].

While cutaneous contact with some allergens such as peanut can cause reactions, the majority of severe or systemic reactions must come from direct ingestion of the allergen[30, 31]. Therefore, the US has strict labelling laws for the eight most common food allergens when present as ingredients. However, reporting use of allergens on shared equipment and in processing are at the discretion of the manufacturer. Among items declaring these advisory statement labels in the US, Ford *et al*[32] found that 5.3 per cent contained detectable residues of allergenic food (ranging in concentration from 3–222 ppm) versus 1.9 per cent among products that lacked a precautionary statement.

Treatment of acute reactions: Prompt administration of intramuscular epinephrine is the first-line therapy for management of food-induced anaphylaxis. Epinephrine is classified by the World Allergy Organization (WAO) as an essential medication for the treatment of anaphylaxis[33]. Injection of a dose of 0.01 mg/kg of 1:1,000 (1 mg/ml) solution to a maximum of 0.5 mg in the lateral thigh (vastus lateralis muscle) is preferred and has been shown to achieve a faster, higher serum medication peak when compared to the administration in the deltoid muscle intramuscularly and to subcutaneous administration[34]. Milder, isolated, non-progressive cutaneous reactions may be treated simply with H1-receptor antagonists. These medications may help to relieve pruritus, hives, angioedema and conjunctivitis,

yet in an anaphylactic reaction, these do not aid with upper airway obstruction, hypotension or shock and are, therefore, not a substitute for epinephrine[33]. However, H1- and H2-receptor antagonists may be used as adjunctive medications during anaphylaxis. Inhaled beta-2 adrenergic agonists have been used for the relief of cough, wheezing and shortness of breath in conjunction with epinephrine, but once again are not a substitute for epinephrine[33]. Other adjuncts include supplemental oxygen and fluids which may be considered after the administration of epinephrine depending on the patient's symptoms.

Oral or intravascular corticosteroids are often administered during an acute reaction with the intent of preventing protracted or biphasic episodes of anaphylaxis. Biphasic reactions are defined as a recurrence of reaction symptoms after the initial anaphylactic reaction has appeared to resolve and occur in 5-7 per cent of all anaphylactic reactions[35,36]. However, retrospective studies are discrepant in whether there is a difference in the rate of biphasic reaction with or without steroid dosing[35,36]. A Cochrane review was unable to identify any quality, relevant studies with evidence for the use of corticosteroids in anaphylaxis and felt unable to either recommend or refute the use of corticosteroids in this instance[37]. It has been noted that the time between onset of symptoms and the initial dose of epinephrine was significantly longer for those patients who did have biphasic reactions[36,38].

Long-term outpatient recommendations: It is the current recommendation that once diagnosed with food allergy the individual avoids all traces of the offending food as well as possible contamination. Patient education should focus on preventing accidental exposures and reading labels to aid in identifying allergenic foods. Given that foods are the most common trigger of anaphylaxis in children, adolescents, and young adults[33], patients must receive instruction on emergency medications and managing home reactions. An emergency healthcare plan in a useful tool to relay this information if presented in a simple, clear manner[39]. Each patient diagnosed with a food allergy should be prescribed self-injectable epinephrine for use in an anaphylactic reaction. In addition, proper device use must be reviewed as one study indicated that although 86 per cent of parents of food allergic children carried the device, only one third were able to correctly administer the medication[40]. In a prospective study of 122 food allergic children prescribed epinephrine, 69 per cent of parents were unable to use the device, did not have it available, or did not know when it should be administered[41]. Families were six times more likely to have received a practical demonstration on epinephrine autoinjector use if the prescribing doctor was a specialist as compared to a general practitioner and 17 times more likely if the physician was an allergy specialist[41].

As reaction severity cannot be predicted from prior reactions or testing, the importance of having self-injectable epinephrine on hand at all times must be imparted to the patient. Risk factors for fatal and near fatal anaphylactic reactions include failure to have epinephrine available, history of prior severe reactions, known food allergy, adolescent age and most importantly asthma[38]. Comorbid asthma, especially poorly controlled asthma, is most often linked to severe reactions[42]. Multiple studies have demonstrated food allergy's effect on quality of life (QoL) measures. In particular, females with food allergy, those with a larger number of food allergies, history of more previous reactions and those with co-existing atopic diseases report poorer QoL[43]. It is to be noted that the prescribing of epinephrine autoinjectors has been found to reduce anxiety in both parents and children though this improvement in anxiety does not improve adherence in carrying the autoinjector[44].

Prevention and treatment

Prevention: The American Academy of Pediatrics (AAP) published updated recommendations in 2008 reviewing nutritional choices in pregnancy, lactation and in the first year of life which may affect development of atopic disease in infants and children[45]. No definitive conclusions have been found regarding maternal dietary exposures during pregnancy and lactation contributing significantly to the development of food allergy in the infant. Therefore, no adjustments to the maternal diet are recommended at this time. While current evidence does support exclusive breastfeeding in high risk infants for at least four months to decrease atopic dermatitis and cow milk allergy in the first two years of life, overall there is little literature supporting the role of breastfeeding in either preventing or delaying the onset of specific food allergies[45,46]. The recommendations note that there is modest evidence that atopic dermatitis may be delayed or prevented by the use of extensively or partially hydrolyzed formulas, compared with cow milk formula, in children unable to be breastfed for the first 4 to 6 months of life[45]. Yet,

the data have not been impressive for the use in the prevention of food allergy.

Timing of the introduction of complementary or solid foods has also been pursued as a factor in the prevention of food allergy in children. However, there is no evidence supporting that delaying introduction beyond 4 to 6 months of age will affect atopy or development of food allergy. Studies looking at early weaning and the development of food allergy in children have actually found a potential protective effect in early weaning. In one study, children introduced to solids at or after 16 wk of age were more likely to have food hypersensitivity and sensitization at one year of age than those weaned prior to 16 wk[47]. More recent data also suggest that delaying the introduction of foods considered highly allergenic may in fact increase the incidence of allergy to these foods[48,49]. The most convincing evidence for early introduction of highly allergenic food proteins and possible oral tolerance comes from a study of the prevalence of peanut allergy in Jewish children in the UK and Israel. Jewish children in the UK were found to have a 10-fold higher prevalence of peanut allergy than those in Israel (1.85 and 0.17%, respectively) where 69 per cent of children ingest peanut by the age of 9 months[48]. The safest way recommended to introduce foods thought to be highly allergenic is at home, in gradually increasing amounts with a rate of introduction of one new food every 3 to 5 days[50].

Several trials underway are addressing this gap in the literature as to whether food introduction plays a role in primary prevention of food allergy including the Starting Time for Allergy Reduction (STAR), Learning Early About Peanut (LEAP), Preventing Peanut Allergy in Atopic Dermatitis (PEAAD), Starting Time for Egg Protein (STEP) and Beating Egg Allergy Trials (BEAT)[50]. Early results from the STAR trial indicate that a high proportion of high risk infants with eczema already have sensitization to foods as well as clinical reactivity prior to the introduction of solid foods at 4 to 5 months of age indicating the possible need for interventions prior to the introduction to solid foods to prevent food allergy[51].

Emerging therapeutics: The possibility of severe fatal reactions with accidental ingestions and lack of standard treatment has led to a strong push to find a viable therapy option for patients. Therapy can be separated into allergen-specific and allergen non-specific immunotherapy. Several small studies have previously been published and now larger, multi-center trials are underway. However, caution must be used when interpreting study results as there is a difference in the outcomes of desensitization and tolerance. Desensitization is a change in the threshold or amount of the allergen needed to induce a reaction whereas tolerance is achieved when one can ingest the allergen on an *ad lib* basis without reaction. Tolerance is a long lasting immunity while with desensitization one must continue to ingest the allergen daily or the immunologic changes may be lost. Induction of tolerance would be considered curative for the food allergy.

Allergen specific therapies include oral immunotherapy (OIT), sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT). OIT involves introducing the food allergen in initial quite low oral doses, and typically escalating the dose over a day or two of rapid dose increase, followed by a slower incremental dose increase over weeks and months. Varying OIT protocols have been used in several small trials showing promise for desensitization to food allergens[52-54]. A multi-center double-blind, randomized, placebo controlled study of OIT in egg allergic children showed both safety and efficacy with a desensitization rate of 75 per cent in the OIT receiving subjects after 22 months of therapy[52]. Peanut OIT has been a particular focus given that peanut is a major cause of food-induced anaphylaxis. However, a recent Cochrane review of peanut OIT trials found only one randomized control trial that resulted in desensitization, yet with a risk of clinically-significant adverse reactions[55]. Though many adverse events have been noted in the studies, especially in the more rapid dose escalation phases, no life threatening event or death has been reported thus far[56]. However, a proportion of patients (~10-20%) in each study appear to be unable to tolerate desensitization due to the side effects of therapy[57]. The Cochrane review authors note that due to the risk of adverse events and current lack of evidence of long-term benefits, peanut OIT cannot currently be recommended without further study[55].

An alternative form of oral therapy exists for cow milk and egg allergy. Subsets of children who are reactive to unheated or lightly cooked egg and milk have been noted to have tolerance of items containing these allergens that are extensively heated. The food protein is thought to be denaturated, with the heat labile protein undergoing a conformational change secondary to the high heat of cooking rendering it to be non allergenic to some patients. Studies have shown that introduction of extensively heated milk and egg appears to hasten the development of tolerance to the

unheated food protein[58-60]. Introduction of extensively heated egg and milk in tolerant children may have immunomodulatory benefit and may potentially be safe in inducing tolerance in the traditional OIT[61].

Similar to OIT, SLIT uses small escalating doses of the food allergen; however, doses are given under the tongue via an extract vehicle. Studies have shown SLIT thus far to be quite safe[62], yet concerns for its efficacy exist as SLIT is unable to achieve the high doses that appear to be necessary in OIT to induce desensitization. The first multi-center, randomized, placebo-controlled study of peanut SLIT showed a modest desensitization at OFC after 44 wk of therapy with 14 of 20 subjects receiving peanut SLIT being able to consume at least a 10-fold increase in the amount of peanut powder they were able to consume when compared to their baseline OFC[63]. The majority of adverse reactions to doses involved the oral-pharyngeal mucosa with only one subject receiving epinephrine at home for oral-pharyngeal symptoms that progressed to cough after antihistamine dosing[63]. In a direct comparison study of SLIT versus OIT for cow milk allergy, systemic reactions were more common with OIT, however, OIT was more efficacious than SLIT alone[64]. However, SLIT remains an appealing therapy to study given it is less likely to cause serious adverse reactions.

Fewer trials so far, have evaluated the administration of allergen via the skin in a patch form in EPIT. In a pilot study using EPIT for the treatment of cow milk allergy, a trend to improvement was noted, but there was no significant increase in the cumulative total dose of cow milk tolerated after three months of therapy with only local reactions being noted[65]. Peanut EPIT has shown promise in mice models of allergy[66,67]. A Phase Ib trial of peanut EPIT in humans showed mostly local, cutaneous adverse events with no significant difference in systemic reactions between the EPIT and placebo groups[68]. Phase II trials are ongoing (Clintrials.gov identifier:NCT01675882). Available from: *http://clinicaltrials.gov/show/NCT1675882 NLM Identifier: NCT1675882*.

Therapies for food allergy in general that are not directed to a specific allergen are also in the midst of study. The food allergy herbal formula-2 (FAHF-2) is a capsule containing a Chinese herbal formula found to abolish anaphylaxis in mice with peanut allergy[69]. Subsequent extended phase I trials in humans showed dosing of the nine herb formula to be both safe and well tolerated over a 6 month period[70]. Phase II efficacy studies are nearing completion. (Clintrials.gov identifiers:NCT00602160, NCT01197053). Available from: *http://clinicaltrials.gov/show/NCT00602160 NLM IdentifierNCT00602160*.

The monoclonal anti-IgE antibody omalizumab has also been found to be a potential non-specific allergen therapy. A multi-center, randomized, double-blind, placebo-controlled phase II trial using omalizumab in the treatment of peanut allergy completed 14 of the planned 150 subjects prior to early discontinuation due to severe anaphylactic reactions during the qualifying OFCs[71]. Of the 14 completing the study, subjects receiving omalizumab trended in tolerating an increased amount of peanut protein following the 24 wk of therapy when compared to placebo[71]. While the data are limited on using omalizumab as a single agent for the treatment of food allergy, focus has shifted to study if omalizumab has a role in OIT, as an adjunct to limit side effects seen in OIT dose escalation. A pilot study using omalizumab as an adjunct to cow milk OIT demonstrated that omalizumab permitted rapid milk dose escalation in a majority of subjects[72]. Multiple centers have elected to study this further. (Clintrial.gov identifiers:NCT01781637, NCT01290913, NCT00932282,NCT01157117). Available from: *http://clinicaltrials.gov/show/NCT01781637 NLM IdentifierNCT01781637*. Available from: *http://clinicaltrials.gov/show/NCT00932282NLM Identifier NCT00932282*. Available from: *http://clinicaltrials.gov/show/NCT01157117 NLM IdentifierNCT01157117*.

Conclusion

Food allergy remains an important health concern due to increasing prevalence worldwide, potentially fatal reactions and current lack of curative therapy. Importance must be placed on proper diagnosis which may at times be difficult given the limitations of current available testing. Avoidance of the offending allergen and prompt treatment of acute reactions are the current mainstays of food allergy management. Present data indicate that there is no benefit in delaying the introduction of allergenic foods to the diet of children. However, much still must be elucidated to understand the optimal timing of allergenic food introduction. While little headway has been made in the prevention of food allergy, multiple therapeutic options including both allergen specific and non-specific therapies are in human efficacy trials. Though the initial results are promising, no single therapy is considered ready for common use until further data on optimal dosing and long-term safety are available.

References

1. NIAID-Sponsord Expert Panel, Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, *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* : S1-58.
2. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, *et al*. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007; *120* : 638-46.
3. Liu AH, Jaramillo R, Sicherer SH, Wood RA, Bock SA, Burks AW, *et al*. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol* 2010;*126* : 798-806.
4. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, *et al*. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol* 2011; *127* : 668-76.
5. Lee AJ, Thalayasingam M, Lee BW. Food allergy in Asia: how does it compare? *Asia Pac Allergy* 2013; *3* : 3-14.
6. Rudders SA, Banerji A, Clark S, Camargo CA Jr. Age-related differences in the clinical presentation of food-induced anaphylaxis. *J Pediatr* 2011; *158* : 326-8.
7. Novembre E, Cianferoni A, Bernardini R, Mugnaini L, Caffarelli C, Cavagni G, *et al*. Anaphylaxis in children: clinical and allergologic features. *Pediatrics* 1998; *101* : E8.
8. Venter C, Arshad SH. Epidemiology of food allergy. *Pediatr Clin North Am* 2011; *58* : 327-49.
9. Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2007; *120* : 1172-7.
10. Savage JH, Matsui EC, Skripak JM, Wood RA. The natural history of egg allergy. *J Allergy Clin Immunol* 2007; *120* : 1413-7.
11. Hajeb P, Selamat J. A contemporary review of seafood allergy. *Clin Rev Allergy Immunol* 2012; *42* : 365-85.
12. Yang MS, Lee SH, Kim TW, Kwon JW, Lee SM, Kim SH, *et al*. Epidemiologic and clinical features of anaphylaxis in Korea. *Ann Allergy Asthma Immunol* 2008; *100* : 31-6.
13. Goh DL, Lau YN, Chew FT, Shek LP, Lee BW. Pattern of food-induced anaphylaxis in children of an Asian community. *Allergy* 1999; *54* : 84-6.
14. Lack G. Update on risk factors for food allergy. *J Allergy Clin Immunol* 2012; *129* : 1187-97.
15. Young E, Stoneham MD, Petruckevitch A, Barton J, Rona R. A population study of food intolerance. *Lancet* 1994; *343* : 1127-30.
16. Shah R, Greenberger PA. Unproved and controversial methods and theories in allergy-immunology. *Allergy Asthma Proce* 2012; *33* (Suppl 1) : S100-2.
17. Adkinson NF, Middleton E. *Middleton's allergy : principles & practice*, 7th ed. Philadelphia: Mosby/Elsevier; 2009.
18. Lieberman JA, Sicherer SH. The diagnosis of food allergy. *Am J Rhinol Allergy* 2010; *24* : 439-43.
19. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy* 2000; *30* : 1540-6.
20. Wang J, Godbold JH, Sampson HA. Correlation of serum allergy (IgE) tests performed by different assay systems. *J Allergy Clin Immunol* 2008; *121* : 1219-24.
21. Sicherer SH, Wood RA; American Academy of Pediatrics Section on Allergy and Immunology. Allergy testing in childhood: using allergen-specific IgE tests. *Pediatrics* 2012; *129* : 193-7.
22. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001; *107* : 891-6.
23. Caubet JC, Sampson HA. Beyond skin testing: state of the art and new horizons in food allergy diagnostic testing. *Immunol Allergy Clin North Am* 2012; *32* : 97-109.
24. Treudler R. Update on *in vitro* allergy diagnostics. *J der Dtsch Dermatol Ges J 2012*; *10* : 89-97.
25. Pongracic JA, Bock SA, Sicherer SH. Oral food challenge practices among allergists in the United States. *J Allergy Clin Immunol* 2012; *129* : 564-6.
26. Jarvinen KM, Sicherer SH. Diagnostic oral food challenges: procedures and biomarkers. *J Immunol Methods* 2012; *383* : 30-8.
27. Jarvinen KM, Amalanayagam S, Shreffler WG, Noone S, Sicherer SH, Sampson HA, *et al*. Epinephrine treatment is infrequent and biphasic reactions are rare in food-induced reactions during oral food challenges in children. *J Allergy Clin Immunol* 2009; *124* : 1267-72.
28. Yu JW, Kagan R, Verreault N, Nicolas N, Joseph L, St Pierre Y, *et al*. Accidental ingestions in children with peanut allergy. *J Allergy Clin Immunol* 2006; *118* : 466-72.
29. Nguyen-Luu NU, Ben-Shoshan M, Alizadehfar R, Joseph L, Harada L, Allen M, *et al*. Inadvertent exposures in children with peanut allergy. *Pediatr Allergy Immunol* 2012; *23* : 133-9.
30. Wainstein BK, Kashef S, Ziegler M, Jelley D, Ziegler JB. Frequency and significance of immediate contact reactions to peanut in peanut-sensitive children. *Clin Exp Allergy* 2007; *37* : 839-45.
31. Simonte SJ, Ma S, Mofidi S, Sicherer SH. Relevance of casual contact with peanut butter in children with peanut allergy. *J Allergy Clin Immunol* 2003; *112* : 180-2.
32. Ford LS, Taylor SL, Pacenza R, Niemann LM, Lambrecht DM, Sicherer SH. Food allergen advisory labeling and product contamination with egg, milk, and peanut. *J Allergy Clin Immunol* 2010; *126* : 384-5.
33. Simons FE, Ardusso LR, Bilo MB, El-Gamal YM, Ledford DK, Ring J, *et al*; World Allergy Organization. World Allergy Organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J* 2011; *4* : 13-37.
34. Simons FE, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *J Allergy Clin Immunol* 2001; *108* : 871-3.
35. Douglas DM, Sukenick E, Andrade WP, Brown JS. Biphasic systemic anaphylaxis: an inpatient and outpatient study. *J Allergy Clin Immunol* 1994; *93* : 977-85.

36. Lee JM, Greenes DS. Biphasic anaphylactic reactions in pediatrics. *Pediatrics* 2000; *106* : 762-6.
37. Choo KJ, Simons E, Sheikh A. Glucocorticoids for the treatment of anaphylaxis: Cochrane systematic review. *Allergy* 2010; *65* : 1205-11.
38. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992; *327* : 380-4.
39. Worth A, Nurmatov U, Sheikh A. Key components of anaphylaxis management plans: consensus findings from a national electronic Delphi study. *JRSM Short Rep* 2010; *1* : 42.
40. Sicherer SH, Forman JA, Noone SA. Use assessment of self-administered epinephrine among food-allergic children and pediatricians. *Pediatrics* 2000; *105* : 359-62.
41. Arkwright PD, Farragher AJ. Factors determining the ability of parents to effectively administer intramuscular adrenaline to food allergic children. *Pediatr Allergy Immunol* 2006; *17* : 227-9.
42. Burks AW, Jones SM, Boyce JA, Sicherer SH, Wood RA, Assa'ad A, *et al*. NIAID-sponsored 2010 guidelines for managing food allergy: applications in the pediatric population. *Pediatrics* 2011; *128* : 955-65.
43. Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. *Allergy* 2010; *65* : 933-45.
44. Cummings AJ, Knibb RC, Erlewyn-Lajeunesse M, King RM, Roberts G, Lucas JS. Management of nut allergy influences quality of life and anxiety in children and their mothers. *Pediatr Allergy Immunol* 2010; *21* : 586-94.
45. Greer FR, Sicherer SH, Burks AW; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008;*121* : 183-91.
46. Gdalevich M, Mimouni D, David M, Mimouni M. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol* 2001; *45* : 520-7.
47. Venter C, Pereira B, Voigt K, Grundy J, Clayton CB, Higgins B, *et al*. Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. *Pediatr Allergy Immunol* 2009; *20* : 320-7.
48. Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, *et al*. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008; *122* : 984-91.
49. Joseph CL, Ownby DrFau-Havstad SL, Havstad SI Fau-Woodcroft Kj Fau-Wegienka G, Wegienka G Fau-Mackechnie H, Mackechnie H Fau- Zoratti E, *et al*. Early complementary feeding and risk of food sensitization in a birth cohort. *20110502DCOM-20110720 [1097-6825 (Electronic)]*.
50. Fleischer DM, Spergel JM, Assa'ad AH, Pongracic JA. Primary prevention of allergic disease through nutritional interventions. *J Allergy Clin Immunol* 2013; *1* : 29-36.
51. Metcalfe J, Prescott SL, Palmer DJ. Randomized controlled trials investigating the role of allergen exposure in food allergy: where are we now? *Curr Opin Allergy Clin Immunol* 2013; *13* : 296-305.
52. Kulis M, Wesley Burks A. Oral immunotherapy for food allergy: Clinical and preclinical studies. *Adv Drug Deliv Rev* 2012; *65* : 774-81.
53. Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, *et al*. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol* 2011; *127* : 654-60.
54. Yeung JP, Kloda LA, McDevitt J, Ben-Shoshan M, Alizadehfar R. Oral immunotherapy for milk allergy. *Cochrane Database Syst Rev* 2012; *11* : CD009542.
55. Nurmatov U, Venderbosch I, Devereux G, Simons FE, Sheikh A. Allergen-specific oral immunotherapy for peanut allergy. *Cochrane Database Syst Rev* 2012; *9* : CD009014.
56. Khoriaty E, Umetsu DT. Oral immunotherapy for food allergy: towards a new horizon. *Allergy Asthma Immunol Res* 2013; *5* : 3-15.
57. Vickery BP. Egg oral immunotherapy. *Curr Opin Allergy Clin Immunol* 2012; *12* : 278-82.
58. Kim JS, Nowak-Wegrzyn A, Sicherer SH, Noone S, Moshier EL, Sampson HA. Dietary baked milk accelerates the resolution of cow's milk allergy in children. *J Allergy Clin Immunol* 2011; *128* : 125-31 e2.
59. Leonard SA, Sampson HA, Sicherer SH, Noone S, Moshier EL, Godbold J, *et al*. Dietary baked egg accelerates resolution of egg allergy in children. *J Allergy Clin Immunol* 2012; *130* : 473-80 e1.
60. Clark A, Islam S, King Y, Deighton J, Szun S, Anagnostou K, *et al*. A longitudinal study of resolution of allergy to well-cooked and uncooked egg. *Clin Exp Allergy* 2011; *41* : 706-12.
61. Huang F, Nowak-Wegrzyn A. Extensively heated milk and egg as oral immunotherapy. *Curr Opin Allergy Clin Immunol* 2012; *12* : 283-92.
62. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W, *et al*. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. *J Allergy Clin Immunol* 2011; *127* : 640-6 e1.
63. Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM, *et al*. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. *J Allergy Clin Immunol* 2013; *131* : 119-27. e1-7.
64. Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, *et al*. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. *J Allergy Clin Immunol* 2012; *129* : 448-55, 455. e1-5.
65. Dupont C, Kalach N, Soulaines P, Legoue-Morillon S, Piloquet H, Benhamou PH. Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. *J Allergy Clin Immunol* 2010; *125* : 1165-7.

66. Mondoulet L, Dioszeghy V, Larcher T, Ligouis M, Dhelft V, Puteaux E, *et al*. Epicutaneous immunotherapy (EPIT) blocks the allergic esophago-gastro-enteropathy induced by sustained oral exposure to peanuts in sensitized mice. *PloS One* 2012; *7* : e31967.

67. Mondoulet L, Dioszeghy V, Ligouis M, Dhelft V, Dupont C, Benhamou PH. Epicutaneous immunotherapy on intact skin using a new delivery system in a murine model of allergy. *Clin Exp Allergy* 2010; *40* : 659-67.

68. Agbotounou W, Martin L, DuPont B, Pascal I, Vauleon C, Benhamou, PH. Epicutaneous Immunotherapy (EPIT) is safe for the treatment of peanut allergy in allergic patients. *J Allergy Clin Immunol* 2013; *131* (Suppl 2) : AB91.

69. Srivastava KD, Kattan JD, Zou ZM, Li JH, Zhang L, Wallenstein S, *et al*. The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in a murine model of peanut allergy. J Allergy Clin Immunol 2005; *115* : 171-8.

70. Patil SP, Wang J, Song Y, Noone S, Yang N, Wallenstein S, *et al*. Clinical safety of Food Allergy Herbal Formula-2 (FAHF-2) and inhibitory effect on basophils from patients with food allergy: Extended phase I study. *J Allergy Clin Immunol* 2011; *128* : 1259-65.

71. Sampson HA, Leung DY, Burks AW, Lack G, Bahna SL, Jones SM, *et al*. A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. *J Allergy Clin Immunol* 2011; *127* : 1309-10.

72. Nadeau KC, Schneider LC, Hoyte L, Borras I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. *J Allergy Clin Immunol* 2011; *127* : 1622-4.

Reprint requests: Dr Rachel Glick Robison, Ann & Robert H. Lurie Children's Hospital of Chicago, Division of Allergy & Immunology, 225 East Chicago Ave, Box 60, Chicago, IL 60611, USA
e-mail: rrobison@luriechildrens.org