

What's new in the diagnosis and management of food allergy in children?

Paul J Turner^{1,2} and Dianne E Campbell^{2,3,*}

¹Imperial College London, London, SW7 2AZ, United Kingdom

²Discipline of Paediatric and Child Health, The University of Sydney, Sydney, NSW 2006, Australia

³Children's Hospital at Westmead, Sydney, NSW 2145, Australia

This article reviews the recent advances in the diagnosis and management of IgE mediated food allergy in children. It will encompass the emerging technology of component testing; moves to standardization of the allergy food challenge; permissive diets which allow for inclusion of extensively heated food allergens with allergen avoidance; and strategies for accelerating tolerance and food desensitization including the use of adjuvants for specific tolerance induction.

Key words: Child; Food; Allergy; Diagnosis

DIAGNOSIS

The gold standard for the diagnosis of IgE mediated food allergy is the double-blind placebo-controlled food challenge (DBPCFC), but in reality this procedure is generally reserved for clinical trials. More commonly utilised are observed food challenges (OFC) usually unblinded to the administering clinician. These are particularly helpful where sensitisation to a food allergen is present – a positive skin prick test (SPT) or detection of serum specific IgE (ssIgE) – without a history of ingestion, or where the history of the ingestion is in doubt, or the history of symptoms resulting from the food ingestion is not highly

suggestive of an IgE mediated reaction.

Most commonly, the clinical diagnosis of food allergy relies upon a convincing recent history of immediate objective symptoms, and the confirmation by detection of IgE production directed against the candidate food, either by SPT and/or by detection of ssIgE.

Two emerging trends have recently influenced the current diagnosis of food allergies, the evolution of component resolved diagnostics (CRD), and the move towards standardisation of protocols, severity indexes and agreed symptoms for OFC and DBPCFC.

Correspondence: Dianne E Campbell
Department of Allergy and Clinical Immunology, Level 3,
Children's Hospital Westmead, Sydney, NSW 2145, Australia
Tel: +61-2-9845-3420
Fax: +61-2-9845-3389
E-mail: Diannec3@chw.edu.au

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Received: March 9, 2013
Accepted: March 17, 2013

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Component testing

Component testing or CRD aims, as the names suggest, to identify and quantitate IgE directed against specific (generally protein) components of each allergen as compared with traditional sIlgE or SPT which assess the presence of IgE to bind to the whole allergen protein sequence and therefore rely on crude allergen extracts. CRD can be performed through the detection of a specific single component of particular interest, such as omega-5-gliadin in wheat dependant exercise induced anaphylaxis (WDEIA), in small panels such as Ara h 1, 2, 3, 8, and 9 in peanut allergy, or increasingly as a microarray, where a large number of recombinant and/or purified components are assayed simultaneously (examples include ISAC microarray).

Peanut

Peanut CRD has been studied most extensively; however its role in the diagnosis of peanut allergy, particularly outside Europe, remains unclear. Research has attempted to correlate reactivity to specific components with clinical allergy (as opposed to sensitisation alone) and/or severity of reaction, as this would improve the ability to prognosticate and reduce the need for OFC. In a number of studies to date Ara h 1, Ara h 2 and Ara h 3 appear to be associated with a higher likelihood of true clinical allergy, whereas reactivity to Ara h 8 is associated with cross sensitisation to birch pollen, and less likely to be associated with significant clinical allergy [1]. Ara h 2, at cut-offs of > 0.1 kUA/L had similar or slightly superior test characteristics (sensitivity, specificity, PPV) compared with SPT and sIlgE when examined in a cohort of Australian infants (12-15 months) with challenge-proven peanut allergy. Importantly however, approximately 20% of infants with challenge-proven peanut allergy had no Ara h 2 detected [2]. Similarly, even using all peanut components, sIlgE and complicated statistical algorithms, the misclassification rate of peanut allergy was still around 7% in a UK based study [3].

Ara h 9 is a member of the heat stable lipid transfer protein (LTP) family (also known as seed storage proteins), and appears to be a regionally important component, relating to cross- and co-sensitisation with similar allergens found, for example, in peach allergic patients in Spain [4] and in oral allergy syndromes. Regional variations in which components appear important in clinical peanut allergy clearly demonstrate the importance of performing region specific studies, before extrapolation of European or North American data to the Asia-pacific region. Importantly, authors of CRD peanut studies generally conclude that detection of specific

components does not rule in or out a clinically important allergy. Sicherer and Wood [5] have recently clearly outlined the situations in which CRD for peanut allergy is most likely to be informative in a comprehensive review of diagnosis of peanut allergy.

Other foods

CRD is useful in the diagnosis of WDEIA where omega-5-gliadin is the most commonly reported component [6]. Other foods have been examined less intensively. Associations have been identified between severity of reactions to soy and Gly m5 and Gly m6 [7]. Ovomuocid (Gal d1) has been associated with clinical reactivity and severity of reaction to extensively heated egg products such as baked cakes and muffins in egg allergic children [8, 9].

Summary statement CRD

The promise of a simple diagnostic test to allow for a highly accurate method of differentiating between clinical relevant IgE mediated allergy and sensitisation alone has yet to be fully realised. Clinicians must be mindful of the pitfalls of over-interpretation of Ara h 2 in particular, but this also applies to CRD for other food allergens. It is likely that as clinical phenotype/component profiles become more extensively defined and regional differences are better understood, more useful applications for CRD will emerge. With the current limited knowledge base, CRD microarray as a screen for potential sensitivities without a high index of suspicion for clinical allergy cannot be recommended. Currently, CRD may be best used judiciously in selected patients for diagnosis of peanut allergy where the a priori likelihood of clinical reactivity is relatively low before proceeding to OFC, in egg allergic children where extensive heated egg OFC is contemplated and in WDEIA. It has not replaced an OFC or DBPCFC in the diagnosis of food allergy.

Standardisation of food challenge protocols and guidelines

Oral food challenge is the gold standard in the diagnosis of food allergy and is also an important tool in safely demonstrating resolution of a known or proven food allergy. With the increasing prevalence of food allergy and testing for IgE sensitisation, and increasing data about decision points at which OFC may be offered for differing food sensitisations, a common uniform national and international standard for OFC is desirable. There have been several important moves towards standardisation of the OFC in recent years, which are helpful not only for clinical trials reporting and harmonising data across study sites and between trials, but also for

improving clinical practice. Standardisation of challenge protocols for particular foods, outlining exact food type and vehicle, dosage schedule and protein content of a complete challenge, will further improve our ability to diagnose and manage children with food allergy.

The 2012 PRACTALL “Standardizing double-blind, placebo-controlled oral food challenges” report [10] is a consensus document produced by the AAAAI and EAACI and is an important step in the standardisation of all OFC. The report includes recommended minimum levels of safety, equipment and personnel, time to observe before discharge following a negative challenge, recommendation of semi-logarithmic dosage scheduling regimes and perhaps most importantly agreed objective criteria for determining a positive challenge reaction. A useful (although not validated) scoring criteria for IgE mediated acute allergic reactions on challenge is presented.

There is no international cross-regional consensus document for standardisation of OFC except the WAO DRACMA report [11], which is specific to cow’s milk allergy, but does outline recommendations for best practice OFC to cow’s milk in a variety of settings.

In our region, efforts to standardise food challenge protocols across countries such as Australia is occurring. The Australian Society for Allergy and Clinical Immunology (ASCI) have now agreed challenge protocols for the most common food allergens, egg, baked egg, milk, wheat, peanut, soy and tree nuts (example of challenge protocol, Supplementary data 1) [12].

MANAGEMENT OF FOOD ALLERGY

The mainstay of management of children with food allergies has been allergen avoidance and provision of action/emergency management plans for accidental exposure to known food allergens (an example of an Australian [ASCI] Management plan is shown in Supplementary data 2). In some instances this also involves the provision of an adrenaline auto injector. More recently, there is an emerging trend towards controlled exposure to the allergen in order to achieve specific tolerance induction, most commonly via the oral route (specific oral tolerance induction, SOTI), and for less restrictive diets for children with egg and milk allergy, with permissive incorporation of heat modified allergen in foods such as cakes and muffins.

Risk management of the food-allergic child

Food allergy is the commonest cause of anaphylaxis in children and can be fatal. Despite the increasing prevalence of food allergy and the incidence of food-induced anaphylaxis [13], the rate of fatal food anaphylaxis remains thankfully low [14, 15]. Nonetheless, allergic individuals and their families often perceive the risk of death to be much greater, resulting in a significant impact on their quality of life. This is partly because affected individuals (or their parents) interpret risk in a more emotion-led context while health professionals often take a rational, objective approach to risk [16].

Measures which may reduce risk of accidental exposure to known food allergens and food anaphylaxis include the provision of clear dietary avoidance instructions, easy-to-follow management plans and education in the use of adrenaline auto-injector devices [17]. A recent study found that provision of adrenaline auto-injector devices increases the impact of the food allergy on quality-of-life measures, although there is an assumption that provision of these medications is an important in reducing the risks of a fatal anaphylactic reaction [18]. Unfortunately there are currently no reliable indicators to accurately predict which food-allergic individuals are more at highest risk of fatal anaphylaxis. Case series fatal food anaphylaxis often quote asthma as a risk factor [14, 19] however the prevalence of asthma is so common that the predictive value for the individual patient is very poor.

There is a tendency to view food-allergic individuals who react to very small levels of allergen (i.e. who have a low eliciting dose or threshold of reactivity) as being more at risk of anaphylaxis. However, a large prospective series of peanut-allergic individuals undergoing DBPCFC did not demonstrate this to be the case [20].

Summary statement risk management

More research is needed to identify strategies to improve risk stratification of food-allergic individuals. Provision of an emergency plan and education regarding dietary avoidance strategies is recommended.

Extensively heat-treated allergens and permissive allergen exposure

Until recently, most allergy guidelines recommended strict avoidance of all forms and amounts of allergen for the diet of allergic children. This was partly on the basis of safety and also on the belief that that accidental allergen exposure may delay the onset of tolerance [21]. It is now widely held that this is unlikely to be the case, with a series of publication demonstrating that most

children allergic to egg and milk can tolerate extensively heated egg and milk in serving size quantities. This is likely to be related to changes in the ability of the allergen to bind specific IgE through heat denaturation of susceptible conformational epitopes. It may also relate to the interaction between the matrix components (such as wheat) and the egg proteins in baked cakes and goods [22].

There are two potential positive effects related the incorporation of extensively heat treated egg and milk in diets of egg and milk allergic children. The first is the lessening on dietary restrictions resulting in improved quality of life. The second is the potential for altering the natural history of the disease, and accelerating acquisition of tolerance to egg and/or milk.

Up to 70% of egg allergic children [23, 24] and milk allergic children [25] will tolerate extensively heated egg or milk in their diet at OFC, whilst still being allergic to the naïve protein. Higher sIgE to ovomucoid appears to be associated with a higher likelihood to being unable to tolerate extensively heated egg in muffin or cake on OFC [8, 26]. Ovomucoid SPT wheal size of > 11 mm has been shown to be associated with more severe generalised allergic reaction on baked muffin OFC [9]. SPT size to egg over time was not shown to be different in children strictly avoiding egg compared with those with regular baked egg ingestion [27] in a recent Australian retrospective study. Although the British Society of Allergy and Clinical Immunology support a home baked egg challenge protocol for selected egg allergic children without a prior history of asthma [28], most other authors and experts recommend that these challenges still take place in a supervised setting, in view of the potential for anaphylaxis [9, 29].

Recently an association between the regular ingestion of clinically tolerated heat-treated egg [30] and milk [25] and a reduction in time to whole milk/egg tolerance has been described in two prospective studies on children consuming regular heated egg or milk following demonstration of tolerance at OFC. Whether this is due to regular ingestion of the heated allergen hastening resolution of the allergy is unknown, as it is possible that children who tolerate extensively heated egg/milk may outgrow their allergy more rapidly irrespective of exposure. Interestingly, these children demonstrate immunological changes consistent with the induction of tolerance, implying the former may be more likely [14, 20]. However as these studies were not randomised controlled trials, no conclusive recommendation can be made at this time to support this as a management strategy purely for the reason of accelerated tolerance.

Finally, although dietary incorporation of extensively-head

modified allergens are likely to become standard practice over the next few years for children with egg and cow milk allergy, there have been a few concerning reports of the development of eosinophilic oesophagitis (EoE) following SOTI to egg [31] and milk [32]. It is possible that EoE could also be precipitated by incorporation of extensively heat-treated egg and milk. Therefore careful follow-up of such patients is advised, with particular attention to any emerging symptoms suggestive of EoE.

Summary statement

Extensively heated egg and milk: Up to 70% of children allergic to egg and cow's milk can tolerate products containing extensively heated egg or milk, such as cake, baked cheese and biscuits. This liberalisation of the diet may have significant gains for patients and families and reduce anxiety around food avoidance. OFC to baked products should be performed in a supervised setting. Anaphylaxis may occur in those children even with a history of non-anaphylactic reactions to the native allergen, and in children without a history of asthma. Careful follow-up is recommended to monitor for any adverse effects.

Specific oral tolerance induction

Much like traditional subcutaneous and sublingual immunotherapy (SLIT) for aeroallergen allergy, immunotherapy for food allergy is based upon administration of gradually increases doses of allergen, most commonly via the oral route, with up-dosing and maintenances phases. Clinical trials to date have tended to be small, with egg, milk and peanut as the most frequently examined allergens. Most published studies have demonstrated a positive effect, although this may be due to a degree of reporting bias associated with negative studies. Primary outcomes have primarily assessed desensitization rather than sustained long term tolerance, and only a few more recent studies have conducted long term follow up [33, 34]. Those studies with follow up have generally shown disappointingly low rates of sustained tolerance, with the vast majority achieving only a temporary state of desensitisation which is rapidly lost without regular ongoing exposure to the allergen [33-35]. The current state of SOTI for food allergens has been comprehensively recently reviewed by several leading food allergy experts [36, 37]. A recent meta-analysis concluded that SOTI cannot currently be recommended for routine clinical practice and that larger, better designed RCTs are required [38].

Egg

Several published studies have examined the efficacy and safety of desensitisation children to egg [34, 35]. The largest and most recent of these examined the effect of daily egg immunotherapy on 55 egg allergic and sensitised children [34]. The study was randomised and blinded during the initial up dosing and maintenance phase (10 months) until the time of the first oral challenge. Children undergoing active treatment continued receiving daily egg in an unblinded fashion until 22 months, were rechallenges and then had a further challenge following 2 months without daily egg. Overall 30 of 40 children were considered to have been desensitised, however only 11 of these children had sustained tolerance following 2 months without the daily egg therapy.

Milk

A 2012 meta-analysis [39] of 5 milk SOTI trials considered to be of suitable quality (out of a total of 16 RCT) concluded that although the quality of evidence was low, desensitisation was achieved in the majority of individuals treated but long term tolerance had not been shown, and that there was a high rate of adverse effects and lack of standardised protocols.

Peanut

A 2012 Cochrane review of SOTI for peanut allergy [40] found only one small peanut SOTI trial (n=28) [41] which satisfied inclusion criteria. SOTI appeared effective for desensitisation, but was associated with a high rate of adverse effects and the authors recommended larger RCT before SOTI for peanut allergy could be recommended.

SOTI with adjuvants

The potential to improve efficacy and safety and to decrease side effects in SOTI has prompted trials involving combination adjuvant and oral immunotherapy protocols.

Anti-IgE therapy and SOTI

Anti-IgE co-administered with milk SOTI has been investigated in a phase one study, and found to be associated with relatively few side effects and allowed desensitisation in the majority of participants [42]. The study requires confirmatory in larger cohorts within a well conducted RCTs. More studies are underway, and preliminary reports suggest a significant improvement in response to SOTI when used in conjunction with anti-IgE

treatment [43]. Mechanistic studies have demonstrated deletion of allergen-specific T cells following high dose cow's milk SOTI and omalizumab therapy, suggesting a plausible rationale for the long term tolerance which is hoped to be obtained using this combination therapy [44].

Probiotics and SOTI

The potential of probiotics co-administered with oral food allergens has been investigated in the murine model where efficacy and protection against experimentally induced food anaphylaxis has been demonstrated [45]. A current clinical trial is underway in a Melbourne based RCT (P-POIT study, ACTRN12608000594325) examining the effectiveness of probiotics and peanut SOTI (P-POIT) in children with peanut allergy.

SOTI- Summary statement

The largest SOTI studies to date have shown effective desensitisation for the majority of patients so long as frequent exposure to the allergen is continued. Sustained tolerance only occurs in a minority of subjects, where long term follow-up has occurred, and this is a significant limitation in its future clinical safety and utility. SOTI requires active and compliant adherence and a willingness to fully participate from patients and their families, and this too may limit its ultimate translational potential. The use of adjuvants in association with SOTI to improve efficiency and safety and decrease side effects is appealing, but not yet proven. Despite the promise of SOTI over the past decade, we are yet to have a reliable, safe, easily-administered SOTI protocol suitable for routine clinical practice in 2013.

Other immunotherapy routes

The finding that patients undergoing birch SLIT were noted to have improvement in their oral allergy symptoms [46] led to the possibility that SLIT might be an effective route for the treatment of other food allergies, where the primary sensitising agents is not an aeroallergen. Small clinical trials utilising food-based SLIT have now shown some efficacy by increasing threshold eliciting doses for allergic reactions to hazelnut [47], peanut [48] and kiwi fruit [49]. Most recently, the trans-epithelial route has been reported in a trial of milk allergic children [50], however no change was noted in the subsequent eliciting dose between control and intervention groups.

Other therapies

Currently under investigation are Chinese herbal preparations, which have been examined at the Mount Sinai centre in New York and collaborating institutions for some years. There is encouraging animal data where the herbal mixture FAHF-2 was demonstrated to completely block experimentally induced peanut anaphylaxis in sensitised mice [51]. Phase 2 human studies are now underway [52].

Allergen-specific T-cell epitopes are targets for a novel potential therapy in food allergy which seeks to induce immunomodulation and oral tolerance by administration of short T-cell epitope peptides, which can target allergen specific T cells without binding IgE. Animal models have demonstrated efficacy [53, 54], and desensitisation has been trialled in human subjects with insect and cat allergy but not, as yet, in food allergy. Promisingly, candidate T cell epitopes for peanut have been identified and research is ongoing [55].

SUMMARY

With the increasing worldwide prevalence of food allergy comes a renewed impetus for improving diagnosis and management. Standardisation of protocols and definitions will assist in the harmonisation and pooling of clinical trial data from disparate sites, and will provide higher quality evidence for both diagnosis and management of paediatric food allergy. Liberalisation of allergen avoidance diets can improve not only the quality of life of children with food allergy, but may hasten their tolerance acquisition. Over the next few decades it is likely that immunotherapy for food allergy will become a standard clinical tool with use of adjuvant co-administration, and will lead to long term sustained tolerance.

SUPPLEMENTARY DATA

Supplementary data are available from: <http://apallergy.org/src/sm/apa-3-88-s001.pdf>.

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