Update on Food Allergy

Rachel L Peters[1,2], Marta Krawiec[3,4,5], Jennifer J Koplin[1,2,6], Alexandra F. Santos[3,4,5,7]

[1]Murdoch Children's Research Institute Melbourne, VIC, Australia

[2]Department of paediatrics, University of Melbourne, Melbourne, VIC, Australia.

[3]Children's Allergy Service, Guy's and St. Thomas' NHS Foundation Trust, London, UK

[4]Department of Women and Children's Health (Paediatric Allergy), School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK

[5]Peter Gorer Department of Immunobiology, School of Immunology and Microbial Sciences, King's College London, London, UK

[6]School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia.

[7]Asthma UK Centre for Allergic Mechanisms of Asthma, London, UK

Corresponding author:

Name: Dr Alexandra Santos

Postal address: Department of Pediatric Allergy, 2nd floor, South Wing, St Thomas' Hospital, 28 Westminster Bridge Road, SE1 7EH London, United Kingdom

Telephone: +44(0)2071886424

Fax: +44(0) 2074038640

Email address: Alexandra.santos@kcl.ac.uk

Word Count: 3860

Number of Tables: 2

Number of Figures: 1

Keywords: food allergy, diagnosis, immunotherapy, biologics, IgE, skin prick test, basophil activation test

Conflicts of interest: Alexandra F. Santos reports grants and personal fees from Medical Research Council (MR/M008517/1); grants from Asthma UK and the NIHR through the Biomedical Research Centre (BRC) award to Guy's and St Thomas' NHS Foundation Trust,

during the conduct of the study; grants from Immune Tolerance Network/National Institute of Allergy and Infectious Diseases (NIAID, NIH), grants from Asthma UK; personal fees from Thermo Scientific, Nutricia, Infomed, Novartis, Allergy Therapeutics, Buhlmann, as well as research support from Buhlmann and Thermo Scientific through a collaboration agreement with King's College London. RLP and JK receive research support from the National Health and Medical Research Council of Australia. The other authors declare no conflicts of interest.

Abstract:

Food allergy is a major public health issue with growing prevalence in the urbanized world and significant impact on the lives of allergic patients and their families. Research into the risk factors that have contributed to this increase and their underlying immune mechanisms could lead us to definitive ways for treatment and prevention of food allergy. For the time being, introduction of peanut and other allergenic foods in the diet at the time of weaning seems to be an effective way to prevent the development of food allergy. Improved diagnosis and appropriate management and support of food allergic patients are central to patient care with food immunotherapy and biologicals making the transition to clinical practice. With the new available treatments it is becoming increasingly important to include patient's and family preferences to provide a management plan tailored to their needs.

Abstract word count: 140

Impact of food allergy

Food allergy (FA) affects about 8% of children in the Western countries and seems to be rising in other parts of the world, particularly in urban rather than rural areas of countries such as Vietnam and South Africa, and other parts of Asia and Africa[1-4]. The prevalence of FA has increased over the recent decades, as have the number of hospitalizations for food-induced anaphylaxis, following what seems to be the "second wave of the allergy epidemic" after the rise in prevalence of asthma and respiratory allergy in previous decades[5-7]. Pouessel et al[8] have shown that foods caused 37% of cases of ICU admissions for anaphylaxis and 79% of recurrent anaphylaxis. Self-reported FA is even more common with an often underappreciated impact[1]. Gupta et al[1] report that about 40% of children report multiple food allergies, often severe food allergies, and carry and adrenaline auto-injector. In Western countries, such as the US and the UK, FA affects disproportionally children from ethnic minorities, such as children of Afro-Caribbean descent[1,9,10]. Whether this has to do with genetic predisposition in face of environmental factors related to the modern life-style or whether the cultural background, the history of inequality and different access to healthcare also play a role, it is unclear[10,11]. The three-fold higher risk of peanut and other food allergies in infants born in Australia to Asian born parents compared with the risk of peanut allergy in infants born to Australian-born parents reinforced this discrepancy reinforce the rapidity with which these changes occur and the importance of gene-environment interactions, that need to be further explored[12].

There is no curative treatment for FA and the mainstay of management is allergen avoidance. Emergency medication needs to be made available to patients to enable them to treat acute allergic reactions that may result from accidental exposure to the culprit allergens, which are unfortunately common[13]. Allergen avoidance imposes dietary restrictions, with potential nutritional consequences and can lead to food insecurity[14-16]. Eighty six per cent of mothers of children with suspected FA avoid foods on their own initiative[17]. Goldberg et al[16] have recently shown that milk allergic young adults have reduced bone mineral density and that low calcium intake, asthma and weight constitute independent risk factors. FA can also result in an impairment of quality of life and mental health of children and their families[17-20]. For instance, mothers of children with suspected FA have higher state and trait anxiety scores than healthy controls[17] and about 50% of children and teenagers with FA experience

bullying[18]. FA can also impact negatively on the costs, not only related to the healthcare but also the indirect costs, for instance related to school and work absences, and the financial burden on the families themselves, resulting for example from the need to spend more time shopping and to find alternative foods, that are often more expensive. All these factors account for additional negative impact on the lives of children with FA and their families, that goes beyond the state of hypersensitivity to the culprit allergens, and underscore the importance of an accurate diagnosis and the search for specific treatments for FA.

Epidemiology

The prevalence of IgE-mediated FA is highest in infancy and early childhood, driven by a relatively high prevalence of egg and cow's milk allergy that often resolves later in childhood. By contrast, peanut and tree nut allergy, which also typically present in infancy, are less likely to resolve and therefore predominate in later childhood[21]. Marked differences in the prevalence of FA between countries have been noted for multiple foods, although data from some countries remains sparse [22-26]. More recent studies have shown that large differences in FA prevalence can exist even within individual countries, with some of this difference driven by a lower prevalence in rural areas compared with urban areas[4,27,28]. Reasons for these differences are largely speculative, with differences in the prevalence of the risk factors described below potentially playing a role.

The strongest known risk factor for FA is probably eczema, particularly eczema which starts early in life and is more severe[27,28]. This finding has been noted consistently across studies in both population-based studies and in allergy clinics for many years; however, the mechanism driving this association remains unclear. It has been hypothesised that a damaged skin barrier resulting from eczema may allow the absorption of food allergens through the skin leading to food sensitisation and allergy, in the absence of pre-existing oral tolerance to those foods[29]. Alternative explanations include the existence of shared genetic or environmental risk factors leading to an increased risk of both eczema and FA.

There has been strong interest in identifying factors that can be modified to prevent FA. Both observational studies and randomised controlled trials have investigated the association between FA and factors including vitamin supplements, fish oil, probiotics and timing of introduction of allergenic foods. These are described further below in the FA prevention

section. Other factors that have been associated with risk of FA include factors potentially associated with increased microbial exposure such as pet dogs and older siblings[30,31].

Mechanisms and pathophysiology

T cells are central coordinators of the immune response to food allergens, namely the production of antibodies by B cells, and understanding the underlying immune mechanism can help us identify targets for treatment and other interventions to prevent and reduce the impact of FA. Using mass cytometry for immunoprofiling of infants, Neeland et al[32] described cellular fingerprints associated with peanut allergy and tolerance amongst IgE sensitised infants. Peanut allergic infants had increased frequency of $CD19^{hi}$HLA-DR^{hi} activated B cells and of peanut-specific memory CD4+ T cells as well as overproduction of TNFalpha whereas peanut sensitised tolerant infants had reduced frequency of CD4+ naïve T cells and an increased frequency of plasmacytoid dendritic cells. Following the description of the new subset of Th2 cells typical of highly allergic patients, the TH2A cells, and that decreased following allergen-specific immunotherapy by Wambre et al[33], Chiang et al[34] found highly differentiated Th2 cells in the peripheral blood of peanut allergic patients that were resistant to the counter effect induced by regulatory T cells whereas healthy controls did not have detectable T cell responses to peanut. A stability of T regulatory response was reported by Weissler et al[35] in both allergic and non-allergic subjects, with a Th2 and Th1-skewed peanut response detected in sensitised and non-sensitised individuals, respectively. However, Pellerin et al found that Tr1 cells were functionally impaired in peanut allergic compared to healthy controls. Ruiter et al[36] studied the TCR repertoire of CD154+CD4+ memory T cells and found strong convergent selection of peanut-specific clones that were more numerous among effector T cells of peanut allergic patients, with an imbalance between effector and regulatory T cells. The more reactive patients had a more diverse and polarised Th2 effector phenotype with the expression of Th2 cytokines correlating with peanut-specific IgE levels.

Recently, new studies have shed light on the role of antibodies in allergy and tolerance and on the still puzzling discrepancy between the presence of allergen-specific IgE and clinical reactivity to foods. For instance, a new subset of T follicular helper cell has been identified in the germinal centre and designated Tfh13 cells[37]. Tfh13 cells are characterised by a distinct transcription factor profile, that includes BCL6 and GATA-3, and by the production of IL-4 and

Il-13. Tfh13 result in high affinity IgE production that is able to induce anaphylaxis to allergens. This high affinity IgE is most likely a result of indirect isotype switching from IgG1+ to IgE+ B cells. Contrary to IgG and IgE that depend on germinal centres and Tfh cells, IgA seems to follow an independent mechanism that requires T cells and CD40-ligand but is independent of germinal centres, Tfh and T follicular regulatory cells[38]. Interestingly, Hoh et al[39] have shown that the class switch recombination from IgG to IgE and the somatic hypermutation that lead to increased affinity for allergens could develop in the gut of peanut allergic individuals, underscoring the importance of gut-associated lymphoid tissue in FA.

Apart from intrinsic characteristics of IgE, like affinity for allergens, post-translational modifications such as glycosylation can have an impact in the ability of IgE to cause effector cell activation and consequently allergic reactions. In a recent study, Shade et al[40] reported that total IgE from peanut allergic had higher sialic acid content compared to non-atopic subjects and that desialylation of IgE reduced effector cell degranulation and consequent anaphylaxis, raising a new possibility for intervention in treating allergic disease, including FA.

These differences in T and B cell responses and antibody profile modulate the effector cell response. Hemmings et al[41] showed that Ara h 2-specific IgE induced greater inhibition of IgE binding and greater mast cell degranulation than Ara h 6, confirming that despite sequence and structural similarities between Ara h 2 and Ara h 6 and the fact that both are major allergens in peanut, Ara h 2 is the dominant allergen. Effector cell response to allergen can support the identification of phenotypes of food allergic patients that may deserve different type of follow up and may have indication for specific treatments, such as allergen-specific immunotherapy or biologics. Patil et al[42] assessed basophil responses to Ara h 2 in peanut allergic patients at baseline and at different time points during peanut oral immunotherapy (OIT). Basophil sensitivity, defined by the concentration at which basophils reacted, after 3 months of OIT, could distinguish the patients who responded had sustained unresponsiveness at the end of the trial from the patients who had transient desensitisation and whose basophil response to Ara h 2 rebounded after stopping OIT.

To conclude, understanding the immune mechanisms underlying FA and oral tolerance is key to improve diagnostics and the care for patients and their families and identify targets for a definitive treatment of FA. Table 1 summarizes recent new discoveries about immune mechanisms of FA.

Diagnosis

An accurate diagnosis of FA is essential. Correctly identifying FA is crucial for providing education and management strategies to mitigate the risks of a potentially life-threatening allergic reactions. In contrast, correctly identifying food tolerance will promote dietary liberation which is especially important in light of the paradigm shift encouraging early introduction of allergenic foods to prevent FA.[43] Double-blind placebo-controlled food challenges remain the gold standard of FA diagnosis. However, due to the inherent risks and intensive resource requirements, their feasibility is limited in some clinical and research settings.

Skin prick tests (SPT) and serum-specific IgE (sIgE) are routinely used in clinical practice and are relatively safe and inexpensive to perform. However, the conventional positive results (SPT ≥ 3mm or sIgE ≥ 0.35ku/l) have poor specificity to clinical FA, with approximately half of sensitised individuals able to tolerate the food without reaction. As increasing magnitude of these tests correlates to a higher risk of reaction, many studies have defined thresholds for these tests with 95% positive predictive value (PPV) to FA (reviewed in [44-49]). Although SPT and sIgE thresholds with 95% PPV to FA are routinely used to minimise the need for diagnostic food challenges, a proportion of children remain in the immunological grey area, that is, they are food sensitised but below the 95% PPV threshold. New approaches that can accurately diagnose FA while reducing the need for food challenges are urgently needed.

Allergen component-resolved diagnostics (CRD) are proposed as a more accurate method of diagnosis, because instead of using crude allergen extracts which consist of both allergenic and non-allergenic components, CRD measures sIgE to individual allergen proteins. A systematic review comparing SPT and sIgE to whole peanut and its components concluded that sIgE to ara h2 had greater diagnostic accuracy compared to the other tests.[47] Furthermore, a meta-analysis of 19 studies found that while sIgE to Arah 1, 2 and 3 had high specificity to peanut allergy, sensitivity was highest Arah 2. The pooled sensitivity and specificity of Arah2 ≥ 0.35kU/L to peanut allergy was 83% (95% CI 76-89%) and 84% (95% CI 77-88%).[50] Likewise, further studies support that component resolved diagnostics offer greater accuracy compares to sIgE to whole allergens for hazelnut [51] and it is plausible that this increased accuracy applies to other foods. The major allergen components for most

common food allergens have been isolated and research continues to identify the optimal cut-off points.[52]

Molecular approaches to the diagnosis of FA also appear to offer greater sensitivity and specificity than traditional tests. The basophil activation test measures the expression of activation markers on the surface of basophils stimulated with food allergens and controls, by flow cytometry.[53] In a study of 109 children, BAT demonstrated superior ability to discriminate between peanut allergic and sensitized- tolerant children compared to SPT, sIgE and sIgE to ara h2. The optimal diagnostic parameter and threshold demonstrated an impressive sensitivity and specificity of 98% (95% CI 87-100) and 96% (95% CI 86-100) respectively. BAT performed similarly well when validated in an independent sample (83% sensitivity and 100% specificity).[54] For other allergens, BAT performed well but not necessarily superior to other measures. In a prospective study of 83 children with suspected tree nut allergy, SPT demonstrated greater sensitivity to BAT, while BAT demonstrated greater specificity compared to SPT; AUC was similar for both measures with the exception of hazelnut where BAT had greater AUC than SPT[55]. While the performance of BAT appears promising, its clinical utility may be limited because it requires live cells and flow cytometry equipment. BAT may therefore be more feasible in settings where it can be used in combination with conventional diagnostic tests. For example, performing peanut BAT as a second step following equivocal SPT or sIgE to Ara h2, reduced the need for OFC by 97% compared to the combination of SPT and sIgE to whole peanut.[54]

Mast cell activation tests offer another promising approach and have the advantage over BAT that they use stored plasma rather than fresh whole blood. In the same sample as described previously for peanut BAT[54] MAT performed equally well to BAT in terms of specificity, however the sensitivity of MAT was lower than BAT. Importantly, MAT provided definitive results in all cases where basophils were non-responsive.[56] In a smaller study, MAT performed better than BAT based on AUC for the diagnosis of peanut allergy, however confidence intervals overlapped.[57] The utility of these test has been assessed for some other common allergens and performs similarly well other further research is needed.[58] Additionally, these molecular approaches may offer additional clinical utility as the results are correlated to reaction severity[57,58], whereas SPT and sIgE are not always predictive of reaction severity[59,60]. However further work is required to inform standardisation of laboratory procedures, optimal

test parameters and thresholds, and cost-effectiveness in different settings before these novel approaches are ready for routine clinical practice.[53]

Despite continued advances and development of novel molecular techniques, identifying a definitive diagnostic test to negate the need for oral food challenges remains elusive. The optimal threshold requires a trade-off between false negatives false positives and this varies in the published literature due to heterogeneity in study sample, design, methods, regional characteristics, allergen extracts and laboratory procedures. Figure 1 represents a suggested approach to the sequential use of diagnostic tests. Identification, validation, and cost-effectiveness of the optimal diagnostic approach for FA continues to be an active area of research.

Treatment

Allergen avoidance

In absence of effective treatment, allergen avoidance and providing appropriate emergency medication used to be the only approach to management of food allergy (FA). [1] Avoidance of food allergen is onerous for patients and families and often fails with ten per cent of patients on average experiencing an allergic reaction per year. [2] [3] [4] Additionally, allergen avoidance inflicts multiple pressures on allergic individuals and their families, food manufacturers and restaurants as well as public spaces such as schools or aircrafts. [5] [6] Precautionary allergen labelling is in general voluntary and used inconsistently across industry which is misleading for patients and caregivers. [2]

Providing adrenaline autoinjectors (AAI) to patients at risk of anaphylaxis encounters challenges related to their availability which is mostly limited to high-income countries, varied national regulations in prescribing and high cost. [7] When prescribed, AAI are only carried at all times by half of the patients [8] and mistakes in use are frequent among both patients [9] and medical staff. [10]

Meeting the needs of both food allergic children undergoing immunotherapy and those continuing strict avoidance in the same environment, e.g. school or household with two allergic siblings managed differently is an arising challenge.

Food immunotherapy

Just over twenty years since the first RCT showed its high efficacy [11], food immunotherapy (FIT) has become the first established treatment modality for food allergy (FA) which is now recommended by national and international guidelines. [12] [13] [14] High efficacy of oral FIT has been consistently confirmed in RCT in children with milk, egg and peanut allergy [15] while slightly lower desensitization rates were achieved in wheat allergy. [16] In the largest oral FIT study so far, the PALISADE Study, which investigated efficacy of 300 mg dose of peanut protein in inducing tolerance to peanut in almost 500 children ≥4 years, 67.2% of participants achieved the primary end point of passing 600 mg dose at the exit DBPCFC. [17] It has also been confirmed recently in a placebo controlled study that peanut oral IT (POIT) significantly reduces the risk of reaction after accidental exposure to peanut (placebo group, 24 reactions in 14 patients; active group, 8 reactions in 5 patients; $p<0.001$). [18]Nevertheless, the recent safety metanalysis which looked into 12 POIT studies estimated that the risk of anaphylaxis while on POIT is over three times higher compared to peanut avoidance (RR, 3.12, 95% CI 1.76-5.55) and the risk of adrenaline use is over twice as high (RR, 2.21; 95% CI 1.27-3.83). [19] Therefore, the current focus of FIT research is orientated towards answering crucial questions about increasing safety of FIT by choosing well-tolerated and effective formulation, route and dose, adding adjuvants at the initial stage of the treatment and identifying patients most likely to benefit from FIT. The other main need is understanding long-term outcomes of the treatment. [20] [21] Table 2 summarises recent developments in FIT and Figure 2 illustrates phenotypes of food allergy and possible outcomes of FIT.

Despite satisfying efficacy in inducing desensitization to the culprit food, the outcome of FIT differs from natural outgrowing of FA. While the benefits of a margin of protection in case of accidental exposure and introducing certain amount of the food in regular diet are enjoyed during the treatment, the long term effect remains unpredictable with up to 70 per cent successfully desensitised individuals losing tolerance after a short period of avoidance.[36] Why the post-IT tolerance is lost despite apparent similarities with outgrowing in immunological response (decrease in specific IgE concentration and raise in specific IgG4), remains unclear.[37] As SU is not achieved by at least half of the patients, the question remains about the necessary frequency of consumption of the food after completion of FIT. Reassuringly, twice a week consumption of an egg has proven sufficient to sustain tolerance in the Spanish SEICAP Study. [39] In the large long-term follow up Finnish cohort of children who completed milk OIT,

only a quarter of the children returned to milk avoidance diet during the median 6.5 yearlong observation period.[40] Regarding ongoing peanut consumption, 64% of previous peanut IT participants continued to ingest peanut daily and another 25% less frequently. Unfortunately, allergic reactions including airway involvement were still noted even in this late stage of desensitization.[41] With the first commercial product for peanut OIT approved by FDA in January 2020, FIT is likely to become more available and uniform in the coming years.

Biologicals

In FA, biological treatments have been mostly investigated in the context of facilitating FIT. In addition to the above mentioned FIT/anti-IgE studies which have already been completed, there are ongoing projects looking at use of dupilumab in combination with peanut OIT (Clinicaltrials.gov NCT03793608, Clinicaltrials.gov NCT03682770), combination of dupilumab and omalizumab in multi-food OIT (Clinicaltrials.gov NCT03679676) as well as anti-IL-33 in peanut OIT (Clinicaltrials.gov NCT02920021). [42]

Due to its patomechanism, eosinophilic pathway inhibition has been extensively studied in the treatment of EoE. [43] The use of anti-IL-5, anti-IL-13 and anti-IL-4 has been associated with significant reduction of histological features of EoE in three RCT. [44] [45] However, there have been no clear clinical improvement noted. Therefore, the treatments are currently not routinely recommended in EoE management. [46]

It has been shown in recent mice study that inhibition of alarmins (IL-25, IL-33 and TSLP) may be effective in preventing FA [47] which may suggest future promising direction of biological use in FA.

Prevention

Despite significant progress in identifying risk factors for FA, there is still little that can be recommended to prevent FA. Few of the known risk factors described above are easily modifiable. Furthermore, of the potentially modifiable factors tested in clinical trials to date, most have not been effective in preventing FA. A recent systematic review by the European Academy of Allergy, Clinical Immunology FA, Anaphylaxis Guidelines Group[108] identified 41 randomised controlled trials of potential FA prevention strategies in infancy and childhood. The vast majority of these trials showed little to no effect on preventing FA, including trials of

dietary avoidance of food allergens, vitamin supplements (maternal and infant), fish oil, probiotics, prebiotics, symbiotics, and hydrolysed formulas. However, the authors also concluded that the evidence around most of these interventions remains very uncertain. Many of the trials were at risk of bias due to lack of robust diagnostic criteria, high loss to follow-up, potential confounding, and lack of blinding and were underpowered for the outcome of interest.

Although some of the risk of FA is likely to be already established at birth, to date there are no known effective preventative strategies that can be applied during pregnancy. The only intervention that is currently widely recommended to reduce the risk of FA is timely introduction of peanut into the infant diet. This recommendation is primarily based on the results of a large, high quality randomised controlled trial in high risk infants conducted in the United Kingdom[9] - a country with a relatively high prevalence of FA. The relevance of these findings to countries with a low peanut allergy prevalence is less clear[109]. There is also evidence from meta-analyses of multiple trials that early introduction of egg into the infant diet reduces the risk of egg allergy, although the extent of the reduction in risk appears lower than for peanut[43].

Conclusion

FA is a major public health issue with growing prevalence in the urbanized world and significant impact on the lives of allergic patients and their families. Research into the risk factors that have contributed to this increase and their underlying mechanisms could pave the way to definitive ways for treatment and prevention of FA. For the time being, introduction of peanut and other allergenic foods in the diet at the time of weaning seems to be an effective way to prevent the development of FA. Improved diagnosis and appropriate management and support of food allergic patients is central to patient care with food immunotherapy and biologicals making the transition to clinical practice. With the new available treatments it is becoming increasingly important to include patient's and family preferences to provide a management plan tailored to their needs.

Tables

Table 1. Highlights of new discoveries about immune mechanisms of food allergy

T cells and T follicular helper cells	• Food allergy involves Th2-skewed response more than a dysregulated regulatory T cell population[34,35]. • The new subset of Tfh cells Tfh13 induces the sequential class switching from IgG1 to IgE leading to the production of high affinity IgE that can cause anaphylaxis[37].
B cells and antibodies	• IgE class switching can happen in the gut-associated lymphoid tissue[39]. • IgA induces tolerance through immune exclusion rather than active suppression and is generated via a separate mechanism that is independent of Tfh and germinal centres[38].
Basophils and mast cells	• IgE glycosylation enhances effector cell degranulation[40]. • Basophil response to allergen can distinguish responders from non-responders as early as 3 months into oral immunotherapy[42].

Table 2. Recent developments in food immunotherapy.

Route	• Safety profile of sublingual IT (SLIT) and epicutaneous IT (EPIT) is favourable with hardly any systemic allergic reactions reported; it comes however at the cost of lower efficacy. [26,27] • In the large phase 3 study on EPIT to peanut, 35.3% of participants achieved predefined response rate compared to 13.6% of children in placebo group; despite the difference being statistically significant, the 95% CI exceeded prespecified lower cut-off which means the study did not meet its primary end point. [28] • The modest level of desensitization predisposes SLIT and EPIT for use in individuals not tolerating OIT. [27] • Longer treatment duration may be necessary to achieve results comparable with OIT. [29]
Dose	• Daily dose equivalent of one peanut and ten peanuts exert similar clinical and immunological effects in peanut IT in young children.[24] • Using lower dose of the food seems to have a favourable effect on safety. No use of adrenaline related to treatment was reported in the recent peanut OIT study in which maintenance peanut protein dose was established between 125 mg and 250 mg.[18] • However, in the group of Japanese children with history of anaphylaxis to wheat, 31% of subjects developed mild anaphylaxis despite low-dose protocol (53 mg of wheat protein). [25]
Age	• FIT tends to be associated with reassuring safety profile and higher rates of sustained unresponsiveness if started early. [24] • In the Italian cohort of 73 infants with IgE-mediated milk allergy who underwent milk OIT, 97% reached the target 150 mL dose of milk. No patient required use of AAI at home. [30]
Formulation	• Well-known phenomenon of decreased allergenicity of thermally processed food [22] has been used in proof of concept FT studies. • The BOPI Study looked into effectiveness and safety of boiled peanut IT. 28% of participants presented with 1.9 episodes of anaphylaxis during treatment which is comparable to average rate of severe adverse events reported in other studies. • Bird *et al* confirmed in a small proof of concept study that baked egg IT led to desensitization to lightly cooked egg with no moderate or severe adverse events noted. [23]

	• The publication of CoFAR7 project comparing baked and fresh egg IT is awaited [ClinicalTrials.gov Identifier: NCT01846208].
Adjuvants	• Multiple adjuvant agents have been tested in the context of improving benefit-risk ratio in FIT, from probiotics and Chinese herb medicine through montelukast and antihistamines to biological treatments.[31] • Anti-IgE has been the most extensively studied including RCTs.[32] • Omalizumab allows quicker up-dosing with fewer adverse events without affecting immunological desensitization processes.[31] • However, omalizumab may potentially mask early symptoms of gastrointestinal disease related to FIT.[33] • Additionally, adverse events may start occurring after discontinuation of anti-IgE in maintenance phase. [34,35]
Sustained unresponsiveness	• The baseline epitope-specific antibody binding models can achieve even 87% accuracy in predicting SU in milk OIT.[38] • In peanut OIT, early decrease in basophil sensitivity to Ara h 2 correlates with SU. [36] • Higher baseline peanut-specific IgG4 to IgE ratio and lower Ara h 2 IgE and basophil activation responses were associated with sustained unresponsiveness in the POISED Study.

Figures and figure legends

Figure 1. Proposed use of components-specific IgE, basophil and mast cell activation tests in combination with conventional tests (skin prick test and specific IgE) to reduce the need for oral food challenges (OFC).

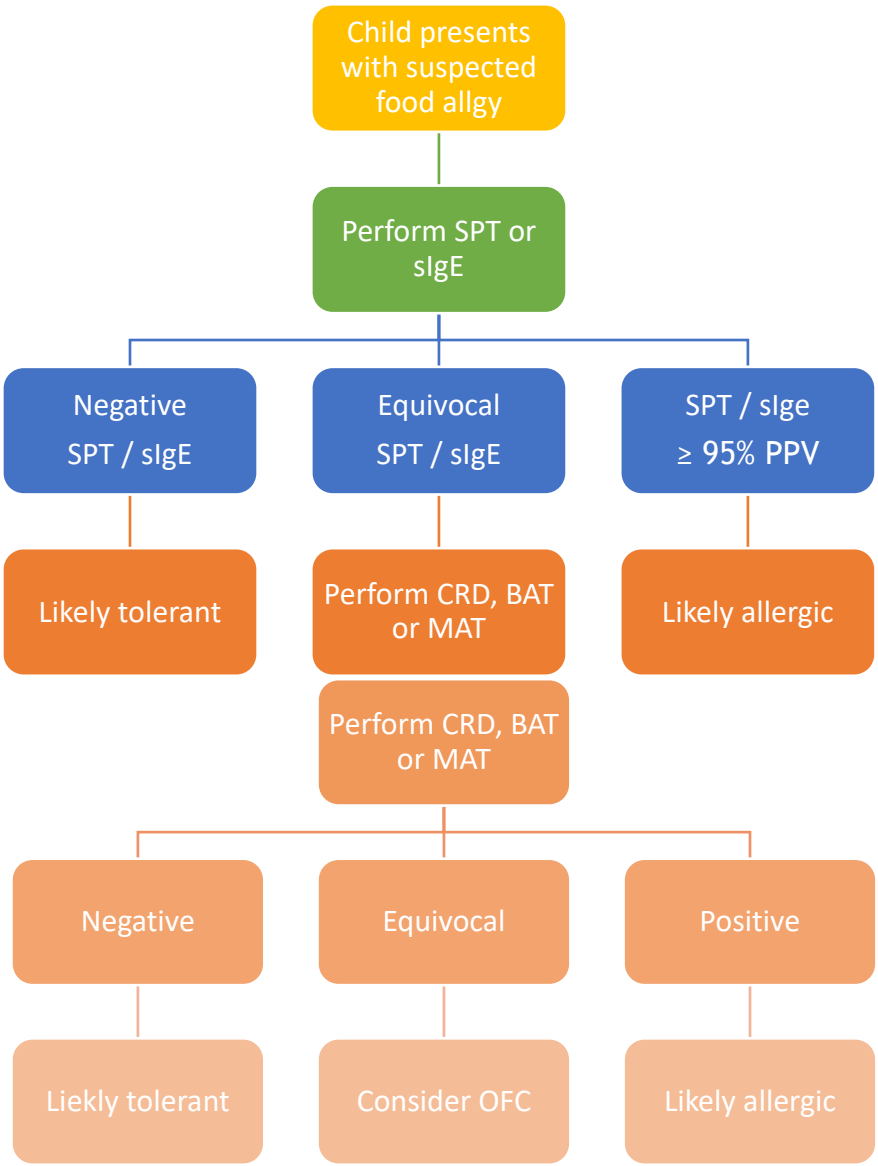
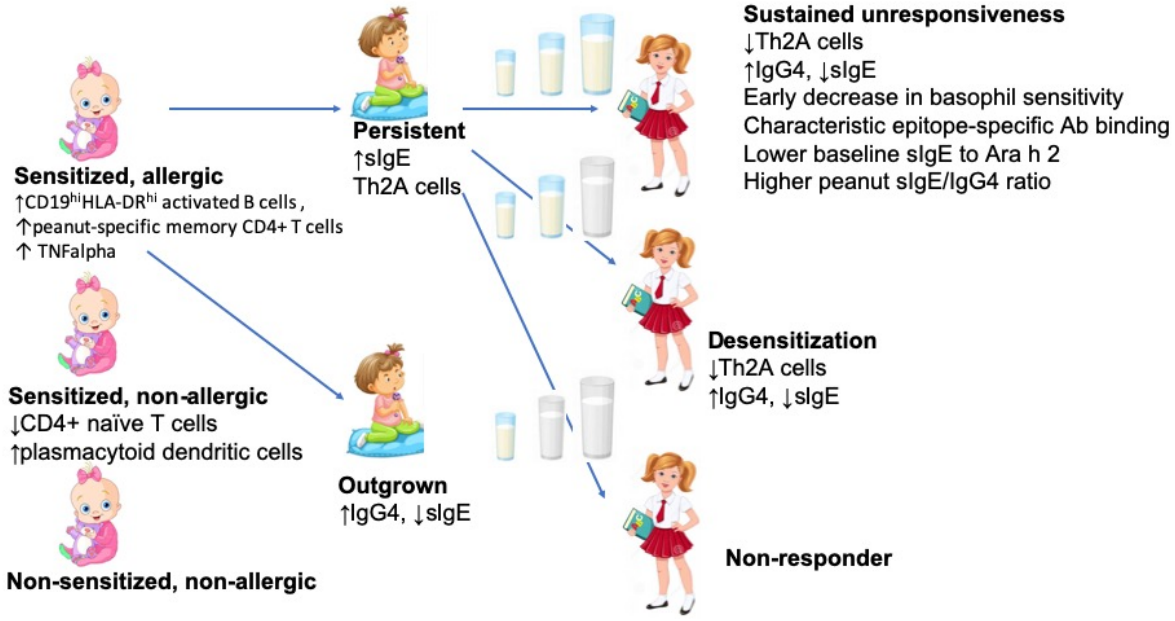


Figure 2. Clinical phenotypes of food sensitized and food allergic children and possible outcomes of food immunotherapy.



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