

A REVIEW OF THE INDUCTION OF TOLERANCE OF IgE-MEDIATED FOOD ALLERGY – PAST, PRESENT AND FUTURE

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ABSTRACT

This article reviews the recent advances and current state of equipoise in the use of immunotherapy for IgE-mediated food allergy. It examines the various methods currently under evaluation for induction of desensitisation and tolerance in food allergy and encompasses permissive diets which allow for inclusion of extensively heated food allergens, specific oral tolerance induction (SOTI), the use of adjuvants for specific tolerance induction and novel pharmacotherapies.

THE PAST-FOOD ALLERGY A RARE MEDICAL ODDITY

The idea of induction of tolerance in food allergy by oral immunotherapy, and the understanding that transient desensitisation and permanent tolerance are quite different, is not new. In 1939, almost 80 years ago, Gert Sydow published a case series of children who most likely had IgE-mediated cow's milk allergy.¹ He showed that children with allergy to cow's milk (CM) could be rendered "insensitive" to the effects of CM if they were exposed at regular and increasing doses of CM. He also reported that whilst temporary tolerance was achievable, long term tolerance was not always possible. Furthermore, he reported that CM could be modified by heating, rendering it non-allergic in some children. This was before the discovery of the elusive "reagin antibody" IgE, in 1966, and before the understanding of what constituted an allergen and how it might be modified in tertiary structure by heat or enzymatic processing. Food allergy, in 1939, was a rare medical oddity, not the epidemic it is today, and as with many insights in medicine, this approach to food allergy was not widely embraced at the time. Thus, this oral approach to desensitisation for food allergy was lost, only to reappear in the first two decades of the next century.

THE PRESENT

The prevalence of IgE-mediated food allergy has alarmingly and dramatically increased over the last 30 years. Whilst the highest rates are reported in countries such as Australia, the UK and USA², there is good evidence to suggest a rise occurring in countries in transition, such as Asia and Africa.³ Along with this rapid increase in the food allergy has come

a demand for services which are currently unmet. This has fostered desire to rethink late 20th century food allergy management of strict avoidance and monitoring for natural tolerance, to interventions which offer the hope of changing natural history and of inducing lifelong tolerance to food allergens in food allergic individuals.

EXTENSIVELY HEAT-TREATED ALLERGENS AND PERMISSIVE ALLERGEN EXPOSURE

In concert with the re-imagining of immunotherapy for food allergy, there has been a paradigm shift in management of food allergy over the last two decades. The previous mantra of strict avoidance of the food allergen has been increasingly challenged. 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 accidental allergen exposure may delay the onset of tolerance.⁴ It is now widely held that this is unlikely to be the case, with a series of publications demonstrating that the majority of children allergic to hen's egg and CM can tolerate extensively heated egg and CM in serving size quantities.

WHAT ARE THE POTENTIAL BENEFITS OF PERMISSIVE ALLERGEN EXPOSURE IN CHILDREN WITH IgE-MEDIATED ALLERGY TO EGG AND CM?

There are potential positive effects which arise from the incorporation of extensively heat treated egg and milk in diets of egg and milk allergic children. The first is the lessening of dietary restrictions, potentially resulting in improved quality of life for both the allergic child and the family. The ability to incorporate extensively-heated CM

("baked" CM) liberalises the diet and also may reduce anxiety over accidental ingestion. Moreover, the benefits of introduction, in terms of reducing anxiety relating to accidental exposure, may indeed be even greater in children with past history of anaphylaxis, where severity of past reaction and length of dietary exclusion has been shown to be associated with reduced quality of life.⁵ Other benefits include the potential for altering the natural history of the disease, and accelerating acquisition of tolerance to egg and/or milk. Whilst high level evidence from well-designed randomised controlled trials is currently lacking, evidence from quasi-controlled trials is suggestive of a positive effect of regular ingestion of baked allergen on time to resolution of egg⁶ and CM allergy.⁷ It has also been suggested that regular ingestion of modified allergens may reduce the risk of severe or even fatal allergic reaction with inadvertent exposures, however this remains hopeful conjecture at this stage.⁸

WHAT ARE THE POTENTIAL RISKS ASSOCIATED WITH PERMISSIVE ALLERGEN EXPOSURE IN CHILDREN WITH IgE-MEDIATED ALLERGY TO EGG AND CM?

Although dietary incorporation of extensively-heated modified allergens are likely to become standard practice over the next few years for children with egg and cow's milk allergy, there have been a few concerning reports of the development of eosinophilic oesophagitis (EoE) following SOTI to egg⁹ and milk.¹⁰ 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.

There is a relatively small but real risk of anaphylaxis on initial challenge to extensively heated egg and CM in those children with IgE-mediated allergy, who have been strictly avoiding all forms of the allergen in their diet, where there is no history of tolerance to modified protein on accidental exposure. Rates of anaphylaxis from previous studies range from 0-6% of total cohorts and up to 20% of all reactors.¹¹⁻¹³ For this reason most experts recommend extensively heated CM and egg oral food challenges (OFC) be performed in medically supervised settings for such allergic children.^{11,14}

MECHANISM OF TOLERANCE TO EXTENSIVELY HEATED ALLERGENS

The mechanism by which CM allergic children may tolerate baked CM, but not other forms of CM, is likely to be related to several factors, including the protein denaturation resulting in conformational changes in the major allergenic epitopes.¹⁵ Tolerance to egg in its baked form may also relate

to the interaction between the matrix components, such as wheat, and the egg proteins in baked cakes and goods¹⁶ and is unlikely to be an effect of a lower dose exposure alone.

Tolerance to heat susceptible allergens may reflect the nature of the underlying allergy, with some evidence to suggest that those who are tolerant to heated CM represent a subgroup of children who have transient, rather than persistent CM allergy.⁷ Children tolerant to baked CM are reported to have less severe reactions to follow-up whole CM challenge than those reacting to baked CM, suggesting that children with CM allergy, who tolerate the baked CM, may represent a different clinical phenotype to their baked CM-allergic counterparts.¹⁷ Moreover CM allergic and egg allergic children who are exposed to frequent baked allergen demonstrate immunological changes consistent with the induction of tolerance, implying a immunotherapeutic effect rather than just cohort selection.^{18,19}

EXTENSIVELY HEAT-TREATED COW'S MILK TOLERANCE IN IgE-MEDIATED CM ALLERGY

Allergy to CM is one of the most common food allergies in childhood and dietary avoidance can be burdensome^{5,20} because of the ubiquitous nature of CM in Western diets. Several groups have reported that up to 75% of CM allergic children (IgE-mediated) can tolerate extensively-heated CM, in baked products such as cakes and biscuits in serving size quantities.^{17,18,21,22} Furthermore, regular ingestion of baked CM products has been shown to potentially accelerate acquisition of tolerance to CM compared with a control group of children who were continuing dietary strict avoidance.⁷

Determining which CM allergic child is likely to be tolerant to baked CM would have significant clinical utility, as outside of some UK centres,²³ most allergists and specialist society guidelines recommend baked CM OFC for children who have been strictly avoiding all CM in their diet, in all forms, should be performed in medically supervised settings.¹⁷ This however places a significant burden on currently overstretched food challenges services, and stratification to determine which children are unlikely to pass baked OFC would be very helpful. Several parameters have been previously reported to be associated with a higher risk of reacting to heat modified CM during OFC, however these parameters do not always allow individual determination of risk.¹⁷ Previous reported predictors of reacting to baked CM include specific IgE reactivity to the heat-stable milk protein casein^{21,22} as well as basophil reactivity.²⁴ We have recently found that CM allergic children with the combination of

multiple IgE-mediated food allergies, asthma and who have had prior anaphylaxis to other foods, appear particularly at risk of reacting to baked CM (in press, *Annals of Asthma Allergy and Immunology*). Although prior anaphylaxis to CM was associated with a higher risk of reacting on baked CM OFC, 60% of children with such a prior history were tolerant at baked milk OFC. Therefore, we have suggested that a past history of CM anaphylaxis is not a contraindication to baked CM OFC.

EXTENSIVELY HEAT-TREATED HEN'S EGG TOLERANCE IN IgE-MEDIATED EGG ALLERGY

Egg is a very common food allergy worldwide and the most common cause of IgE-mediated food allergy in Australian infants, with a prevalence of 9%.²⁵ Up to 70% of egg allergic children tolerate extensively heated egg in their diet at OFC, whilst still being allergic to the native protein as we¹¹ and others have previously shown.^{12,13,18}

Higher sIgE to ovomucoid appears to be associated with a higher likelihood of being unable to tolerate extensively heated egg in muffin or cake on OFC.^{26,27} Ovomucoid SPT wheal size of >11 mm has been shown to be associated with more severe generalised allergic reaction on baked muffin OFC.²⁸ Although the British Society of Allergy and Clinical Immunology (BSACI) support a home baked egg challenge protocol for selected egg allergic children without a prior history of asthma,²⁹ most other authors and experts recommend that these challenges still take place in a supervised setting, in view of the potential for anaphylaxis.^{14,28}

SPECIFIED ORAL TOLERANCE INDUCTION (SOTI)

SOTI has become of intense interest to patients, the media and the food industry. Much like traditional subcutaneous and sublingual immunotherapy for aeroallergen and venom allergy, immunotherapy for food allergy is based upon administration of gradually increased doses of allergen, most commonly via the oral route, with up-dosing and maintenance phases. Clinical trials to date have tended to be small, with egg, milk and peanut as the most frequently examined allergens. Randomised Controlled Trials (RCT) have shown SOTI with egg, cow's milk and peanut can induce desensitisation in a significant proportion of allergic children.³⁰ However, most SOTI studies to date report high rates of adverse events during SOTI, causing withdrawals of up to 10-20% of patients, with up to one quarter of subjects suffering frequent adverse reactions.

The current state of SOTI for food allergens has recently been comprehensively reviewed by several leading food allergy experts.^{31,32} A recent meta-analysis concluded that SOTI cannot currently be recommended for routine clinical practice and that larger, better designed RCTs are required.³³ However, pressure is such that SOTI is currently being conducted outside of research studies and trials as a clinical therapy in some centres,³⁴ despite urging from most experts to not rush into suboptimal practices without a high level evidence base.³⁵⁻³⁷ Despite this, in most regions access to SOTI for food allergic patients remains currently limited to participation in clinical trials.

DESENSITISATION OR LONG TERM TOLERANCE WITH SOTI?

Most primary outcomes in SOTI studies have assessed desensitisation rather than sustained long term tolerance and only a few more recent studies have conducted long term follow up. 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.³⁸⁻⁴⁰ Most recently reported is data from an open cohort study now in its 5th year, demonstrating long term tolerance, after being off daily therapy for one month, in 12 of 39 peanut allergic subjects enrolled in open peanut SOTI pilot, 24 of whom reached desensitisation.⁴¹ The Immune Tolerance Network IMPACT trial is evaluating long-term tolerance among children with peanut allergy in a randomised 3-year peanut OIT trial to further address this issue.⁴²

MECHANISM OF INDUCTION OF TOLERANCE - SOTI

Markers of desensitisation and tolerance in SOTI have been reported by a number of groups. In general, SOTI is associated with an early increase in allergen specific IgE levels with low dose allergen and then a plateau and later decrease, to less than pre-treatment levels. In association, allergen specific IgG4 is often noted to increase over the course of successful immunotherapy treatment.⁴³ Reduction in epitope diversity with long term SOTI has been reported⁴⁴ and reduction in reactivity in the basophil activation test (BAT) also appears to correlate with successful induction of desensitisation.⁴⁵

Induction of allergen specific T-regulatory cell populations may be important for desensitisation,⁴⁶ although some studies have failed to find significant Treg induction as a marker for successful tolerance.⁴¹ Predictors of sustained unresponsiveness in long term peanut SOTI are reported

to be baseline peanut-specific IgE/total IgE ratio, whereas in the same study, reduction in Ara h2-specific IgE level at end of therapy best correlated with sustained tolerance to peanut. Peanut-specific IgG4 was not a useful predictor of tolerance in this cohort.⁴¹

EGG SOTI

Several published studies have examined the efficacy and safety of desensitising children to egg.^{39,40} The largest and most recent of these examined the effect of daily egg immunotherapy on 55 egg allergic and sensitised children.⁴⁰ 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 then continued receiving daily egg in an unblinded fashion until 22 months, were rechallenged 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 SOTI

A 2012 meta-analysis⁴⁷ 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 there was a high rate of adverse effects and lack of standardised protocols.

PEANUT SOTI

A 2012 Cochrane review of SOTI for peanut allergy⁴⁸ found only one small peanut SOTI trial (n=28)⁴³ 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. A 2014 meta-analysis included 3 studies (SLIT and OIT with a total 86 participants) and concluded that a significant effect on desensitisation was found but that further larger studies were required.³⁵ Subsequently the STOP II trial was published, which reported less side effects in a RCT of 99 peanut allergic children, as determined for inclusion into the study by DBFC, using a lower dose and longer up-dosing regimen. Desensitisation was confirmed for 62% (24 of 39 participants). The maximum daily peanut maintenance in this study was 800 mg, and the cumulative total food challenge dose was 1.4 g peanut protein. This is a low total cumulative dose, and may have skewed the true desensitisation rate, with changes in threshold rather than

actual desensitisation, in some children. Moreover, long term tolerance was not assessed, as the authors state based upon previous studies, it was unlikely to be successful.⁴⁹

MULTIPLE FOODS SOTI

A recent phase one safety and feasibility trial in which food allergy children undertook daily multiple food SOTI (n=25) reported feasibility with multiple foods, with longer up-dosing phases required, but similar overall safety compared with those children undergoing peanut SOTI alone (n=15).⁵⁰

MODIFIED PEANUT AND SOTI

We have recently shown that boiled peanut may offer a potential alternative to roasted or raw peanut SOTI. Boiling of peanuts has been shown to reduce the 2S globulins and Ara h2/6 and removes significant amounts of protein from the peanuts into the boiling water.⁵¹ We identified a small number of children who were either de novo boiled peanut tolerant, or tolerant following exposed to regular increasing amounts of boiled peanut. These patients had significant reactivity to Ara h2, which may explain why they tolerate boiled peanut with little side effects. (In press, JACI). Based upon these preliminary results, a RCT of boiled peanut for children with peanut allergy is currently in progress in Australia and the UK (BOPI-ACTRN-12614000265673).

Other approaches to modification of peanut protein have been reported to offer potential benefits over traditional SOTI. Polyphenolic phytochemicals, which have high affinity to bind proteins and form soluble and insoluble complexes, have been shown to reduce in vitro IgE binding and reduce basophil degranulation.⁵²

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. These include:

Biologics and SOTI

There are now a number of reports of the use of anti-IgE co-administered with SOTI in an attempt to accelerate up-dosing schedule⁵³ and/or reduce side effects and improve efficacy.⁵⁴ A phase one CM study reported relatively few side effects and allowed desensitisation in the majority of participants.⁵⁵ Similar results were reported from phase one study using omalizumab with multiple food SOTI.⁵⁶ 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.⁵⁷ Overall, the use of anti-IgE in combination with SOTI requires confirmation in larger cohorts within well conducted RCTs. In addition, other biologic agents such as interferon-gamma⁵⁸ have been trialled as adjunct therapy in SOTI.

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.⁵⁹ A current clinical trial is underway in a Melbourne, Australia based RCT (P-POIT study, ACTRN12608000594325) examining the effectiveness of probiotics and peanut SOTI (P-POIT) in children with peanut allergy.

Other adjuvants

A multitude of other adjuvants have been considered for potential use for food allergy immunotherapy. These include chitosan, CpG motifs and parasites and are detailed in a recent review of emerging therapies for food allergy.⁶⁰

OTHER IMMUNOTHERAPY ROUTES

The finding that patients undergoing birch sublingual immunotherapy (SLIT) were noted to have improvement in their oral allergy symptoms⁶¹ led to the possibility that SLIT might be an effective route for the treatment of other food allergies, where the primary sensitising agent 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 CM,³⁸ hazelnut,⁶² peanut⁶³ and kiwi fruit.⁶⁴ Most recently, the trans-epithelial route has been reported in a trial of milk allergic children,⁶⁵ however no change was noted in the subsequent eliciting dose between control and intervention groups. A phase 2 trial of epicutaneous peanut immunotherapy within the CoFAR network is currently underway (ClinicalTrials.gov identifier: NCT01904604).

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.⁶⁶ Phase 2 human studies are now underway.⁶⁷

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,^{68,69} 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 on-going.⁷⁰

THE FUTURE

With the increasing worldwide prevalence of food allergy comes a renewed impetus for targeting disease modification rather than simply allergen avoidance. Standardisation of study protocols will assist in the harmonisation and pooling of clinical trial data from RCT of immunotherapy and will provide higher quality evidence for the induction of tolerance in food allergy. Liberalisation of allergen avoidance diets can not only improve the quality of life of children with food allergy, but may hasten or alter tolerance acquisition. Whereas SOTI is currently recommended in the research setting only, over the next few decades it is likely that immunotherapy for food allergy will become a standard clinical tool using adjuvant and modified allergens, which will provide sustained tolerance rather than transient desensitisation for the majority of food allergy individuals.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest.

REFERENCES

1. G S. Some Cases of Cow's Milk Idiosyncrasy. *Acta Paediatrica*. 1939;23(3):383-96.
2. Prescott S, Allen KJ. Food allergy: riding the second wave of the allergy epidemic. *Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology*. 2011;22(2):155-60. Epub 2011/02/22.
3. Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn J, Fiocchi A, et al. A global survey of changing patterns of food allergy burden in children. *The World Allergy Organization journal*. 2013;6(1):21. Epub 2013/12/07.
4. Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. *J Pediatr*. 1989;115(1):23-7. Epub 1989/07/01.
5. Indinnimeo L, Baldini L, De Vittori V, Zicari AM, De Castro G, Tancredi G, et al. Duration of a cow-milk exclusion diet worsens parents' perception of quality of life in children with food allergies. *BMC pediatrics*. 2013;13:203. Epub 2013/12/07.
6. Leonard SA, Sampson HA, Sicherer SH, Noone S, Moshier EL, Godbold J, et al. Dietary baked egg accelerates resolution of egg allergy in children. *The Journal of allergy and clinical immunology*. 2012;130(2):473-80 e1. Epub 2012/08/01.
7. 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. *The Journal of allergy and clinical immunology*. 2011;128(1):125-31 e2. Epub 2011/05/24.
8. Turner PJ, Boyle RJ. Food allergy in children: what is new? Current opinion in clinical nutrition and metabolic care. 2014;17(3):285-93. Epub 2014/03/13.
9. Ridolo E, De Angelis GL, Dall'aglio P. Eosinophilic esophagitis after specific oral tolerance induction for egg protein. *Ann Allergy Asthma Immunol*. 2011;106(1):73-4. Epub 2011/01/05.
10. Sanchez-Garcia S, Rodriguez Del Rio P, Escudero C, Martinez-Gomez MJ, Ibanez MD. Possible eosinophilic esophagitis induced by milk oral immunotherapy. *J Allergy Clin Immunol*. 2012;129(4):1155-7. Epub 2012/01/13.
11. Turner PJ, Mehr S, Joshi P, Tan J, Wong M, Kakakios A, et al. Safety of food challenges to extensively heated egg in egg-allergic children: a prospective cohort study. *Pediatric allergy and immunology: official publication of the*

- European Society of Pediatric Allergy and Immunology. 2013;24(5):450-5. Epub 2013/06/19.
12. 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. Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology. 2011;41(5):706-12. Epub 2011/04/15.
13. Lieberman JA, Huang FR, Sampson HA, Nowak-Wegrzyn A. Outcomes of 100 consecutive open, baked-egg oral food challenges in the allergy office. The Journal of allergy and clinical immunology. 2012;129(6):1682-4 e2. Epub 2012/06/05.
14. Leonard SA, Nowak-Wegrzyn A. Re-defining food allergy phenotypes and management paradigm: is it time for individualized egg allergy management? Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology. 2011;41(5):609-11. Epub 2011/04/15.
15. Nowak-Wegrzyn A, Fiocchi A. Rare, medium, or well done? The effect of heating and food matrix on food protein allergenicity. Current opinion in allergy and clinical immunology. 2009;9(3):234-7. Epub 2009/05/16.
16. Shin M, Lee J, Ahn K, Lee SI, Han Y. The influence of the presence of wheat flour on the antigenic activities of egg white proteins. Allergy, asthma & immunology research. 2013;5(1):42-7. Epub 2013/01/02.
17. Nowak-Wegrzyn A, Bloom KA, Sicherer SH, Shreffler WG, Noone S, Wanich N, et al. Tolerance to extensively heated milk in children with cow's milk allergy. The Journal of allergy and clinical immunology. 2008;122(2):342-7, e1-2. Epub 2008/07/16.
18. Lemon-Mule H, Sampson HA, Sicherer SH, Shreffler WG, Noone S, Nowak-Wegrzyn A. Immunologic changes in children with egg allergy ingesting extensively heated egg. The Journal of allergy and clinical immunology. 2008;122(5):977-83 e1. Epub 2008/10/15.
19. Huang F, Nowak-Wegrzyn A. Extensively heated milk and egg as oral immunotherapy. Current opinion in allergy and clinical immunology. 2012;12(3):283-92. Epub 2012/04/18.
20. Sicherer SH, Noone SA, Munoz-Furlong A. The impact of childhood food allergy on quality of life. Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology. 2001;87(6):461-4. Epub 2002/01/05.
21. Caubet JC, Nowak-Wegrzyn A, Moshier E, Godbold J, Wang J, Sampson HA. Utility of casein-specific IgE levels in predicting reactivity to baked milk. The Journal of allergy and clinical immunology. 2013;131(1):222-4 e1-4. Epub 2012/08/28.
22. Bartnikas LM, Sheehan WJ, Hoffman EB, Permaul P, Dioun AF, Friedlander J, et al. Predicting food challenge outcomes for baked milk: role of specific IgE and skin prick testing. Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology. 2012;109(5):309-13 e1. Epub 2012/10/16.
23. Luyt D, Ball H, Makwana N, Green MR, Bravin K, Nasser SM, et al. BSACI guideline for the diagnosis and management of cow's milk allergy. Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology. 2014;44(5):642-72. Epub 2014/03/05.
24. Ford LS, Bloom KA, Nowak-Wegrzyn AH, Shreffler WG, Masilamani M, Sampson HA. Basophil reactivity, wheal size, and immunoglobulin levels distinguish degrees of cow's milk tolerance. The Journal of allergy and clinical immunology. 2013;131(1):180-6 e1-3. Epub 2012/07/24.
25. 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 criteria in infants. The Journal of allergy and clinical immunology. 2011;127(3):668-76 e1-2. Epub 2011/03/08.
26. Caubet JC, Bencharitiwong R, Moshier E, Godbold JH, Sampson HA, Nowak-Wegrzyn A. Significance of ovomucoid- and ovalbumin-specific IgE/IgG(4) ratios in egg allergy. J Allergy Clin Immunol. 2012;129(3):739-47. Epub 2012/01/27.
27. Ando H, Moverare R, Kondo Y, Tsuge I, Tanaka A, Borres MP, et al. Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy. J Allergy Clin Immunol. 2008;122(3):583-8. Epub 2008/08/12.
28. Tan JW, Campbell D, Turner P, Kakakios A, Wong M, Mehr S, et al. Baked Egg Food Challenges - Clinical Outcomes And Determination Of Negative And Positive Predictive Values For Skin Test To Baked Egg And Ovomucoid. The Journal of allergy and clinical immunology. 2012;129(2):AB22.
29. Clark AT, Skypala I, Leech SC, Ewan PW, Dugue P, Brathwaite N, et al. British Society for Allergy and Clinical Immunology guidelines for the management of egg allergy. Clin Exp Allergy. 2010;40(8):1116-29. Epub 2010/07/24.
30. Tang ML, Martino DJ. Oral immunotherapy and tolerance induction in childhood. Pediatr Allergy Immunol. 2013;24(6):512-20. Epub 2013/08/03.
31. Ismail IH, Tang ML. Oral immunotherapy for the treatment of food allergy. Isr Med Assoc J. 2012;14(1):63-9. Epub 2012/05/26.
32. Khoriaty E, Umetsu DT. Oral immunotherapy for food allergy: towards a new horizon. Allergy Asthma Immunol Res. 2013;5(1):3-15. Epub 2013/01/02.
33. Fisher HR, du Toit G, Lack G. Specific oral tolerance induction in food allergic children: is oral desensitisation more effective than allergen avoidance?: a meta-analysis of published RCTs. Arch Dis Child. 2011;96(3):259-64. Epub 2010/06/05.
34. Wasserman RL, Factor JM, Baker JW, Mansfield LE, Katz Y, Hague AR, et al. Oral immunotherapy for peanut allergy: multipractice experience with epinephrine-treated reactions. The journal of allergy and clinical immunology In practice. 2014;2(1):91-6. Epub 2014/02/26.
35. Sun J, Hui X, Ying W, Liu D, Wang X. Efficacy of allergen-specific immunotherapy for peanut allergy: a meta-analysis of randomized controlled trials. Allergy and asthma proceedings: the official journal of regional and state allergy societies. 2014;35(2):171-7. Epub 2014/04/11.
36. Wood RA, Sampson HA. Oral immunotherapy for the treatment of peanut allergy: is it ready for prime time? The journal of allergy and clinical immunology In practice. 2014;2(1):97-8. Epub 2014/02/26.
37. Sampson HA. Peanut oral immunotherapy: is it ready for clinical practice? The journal of allergy and clinical immunology In practice. 2013;1(1):15-21. Epub 2013/11/16.
38. Keet CA, Frischmeyer-Guerrero 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(2):448-55, 55 e1-5. Epub 2011/12/02.
39. Staden U, Rolinck-Werninghaus C, Brewe F, Wahn U, Niggemann B, Beyer K. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. Allergy. 2007;62(11):1261-9. Epub 2007/10/09.
40. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, et al. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med. 2012;367(3):233-43. Epub 2012/07/20.
41. Vickery BP, Scurlock AM, Kulis M, Steele PH, Kamilaris J, Berglund JP, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. J Allergy Clin Immunol. 2014;133(2):468-75. Epub 2013/12/24.
42. Jones SM, Burks AW, Dupont C. State of the art on food allergen immunotherapy: oral, sublingual, and epicutaneous. The Journal of allergy and clinical immunology. 2014;133(2):318-23. Epub 2014/03/19.
43. 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(3):654-60. Epub 2011/03/08.
44. Vickery BP, Lin J, Kulis M, Fu Z, Steele PH, Jones SM, et al. Peanut oral immunotherapy modifies IgE and IgG4 responses to major peanut allergens. J Allergy Clin Immunol. 2013;131(1):128-34 e1-3. Epub 2012/12/04.
45. Vila L, Moreno A, Gamboa PM, Martinez-Aranguren R, Sanz ML. Decrease in antigen-specific CD63 basophil expression is associated with the development of tolerance to egg by SOTI in children. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology. 2013;24(5):463-8. Epub 2013/05/21.
46. Syed A, Garcia MA, Lyu SC, Bucayu R, Kohli A, Ishida S, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). J Allergy Clin Immunol. 2014;133(2):500-10. Epub 2014/03/19.
47. Yeung JP, Kloda LA, McDevitt J, Ben-Shoshan M, Alizadehfar R. Oral immunotherapy for milk allergy. Cochrane Database Syst Rev. 2012;11:CD009542. Epub 2012/11/16.
48. Nurmatov U, Venderbosch I, Devereux G, Simons FE, Sheikh A. Allergen-specific oral immunotherapy for peanut allergy. Cochrane Database Syst Rev. 2012;9:CD009014. Epub 2012/09/14.
49. Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet. 2014;383(9925):1297-304. Epub 2014/02/04.
50. Begin P, Winterroth LC, Dominguez T, Wilson SP, Bacal L, Mehrotra A, et al. Safety and feasibility of oral immunotherapy to multiple allergens for food allergy. Allergy, asthma, and clinical immunology: official journal of the Canadian Society of Allergy and Clinical Immunology. 2014;10(1):1. Epub 2014/01/17.
51. Beyer K, Morrow E, Li XM, Bardina L, Bannon JA, Burks AW, et al. Effects of cooking methods on peanut allergenicity. J Allergy Clin Immunol. 2001;107(6):1077-81. Epub 2001/06/09.
52. Plundrich NJ, Kulis M, White BL, Grace MH, Guo R, Burks AW, et al. Novel Strategy To Create Hypoallergenic Peanut Protein-Polyphenol Edible Matrices for Oral Immunotherapy. J Agric Food Chem. 2014. Epub 2014/04/25.
53. Schneider LC, Rachid R, LeBovidge J, Blood E, Mittal M, Umetsu DT. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. J Allergy Clin Immunol. 2013;132(6):1368-74. Epub 2013/11/02.
54. Dominguez T. The Safety of Multiple Oral Immunotherapy In Phase one Studies At A Single Center. EAACI Food Allergy & Anaphylaxis Meeting 20132013.
55. 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(6):1622-4. Epub 2011/05/07.
56. Begin P, Dominguez T, Wilson SP, Bacal L, Mehrotra A, Kausch B, et al. Phase

- 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using Omalizumab. *Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology*. 2014;10(1):7. Epub 2014/03/01.
57. Bedoret D, Singh AK, Shaw V, Hoyte EG, Hamilton R, DeKruyff RH, et al. Changes in antigen-specific T-cell number and function during oral desensitization in cow's milk allergy enabled with omalizumab. *Mucosal Immunol*. 2012;5(3):267-76. Epub 2012/02/10.
58. Noh G, Jang EH. Dual specific oral tolerance induction using interferon gamma for IgE-mediated anaphylactic food allergy and the dissociation of local skin allergy and systemic oral allergy: tolerance or desensitization? *Journal of investigational allergology & clinical immunology*. 2014;24(2):87-97. Epub 2014/05/20.
59. Schouten B, van Esch BC, Hofman GA, van Doorn SA, Knol J, Nauta AJ, et al. Cow milk allergy symptoms are reduced in mice fed dietary synbiotics during oral sensitization with whey. *J Nutr*. 2009;139(7):1398-403. Epub 2009/05/29.
60. Keet CA, Wood RA. Emerging therapies for food allergy. *The Journal of clinical investigation*. 2014;124(5):1880-6. Epub 2014/05/03.
61. Asero R. Effects of birch pollen-specific immunotherapy on apple allergy in birch pollen-hypersensitive patients. *Clin Exp Allergy*. 1998;28(11):1368-73. Epub 1998/11/21.
62. Enrique E, Pineda F, Malek T, Bartra J, Basagana M, Tella R, et al. Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. *J Allergy Clin Immunol*. 2005;116(5):1073-9. Epub 2005/11/09.
63. Fleischer Dm Fau - Burks AW, Burks Aw Fau - Vickery BP, Vickery Bp Fau - Scurlock AM, Scurlock Am Fau - Wood RA, Wood Ra Fau - Jones SM, Jones Sm Fau - Sicherer SH, et al. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. (1097-6825 (Electronic)).
64. Mempel M, Rakoski J, Ring J, Ollert M. Severe anaphylaxis to kiwi fruit: Immunologic changes related to successful sublingual allergen immunotherapy. *J Allergy Clin Immunol*. 2003;111(6):1406-9. Epub 2003/06/06.
65. Dupont C, Kalach N, Soulaïnes 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(5):1165-7. Epub 2010/05/11.
66. 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(1):171-8. Epub 2005/01/08.
67. Wang J, Li XM. Chinese herbal therapy for the treatment of food allergy. *Curr Allergy Asthma Rep*. 2012;12(4):332-8. Epub 2012/05/15.
68. Yang M, Yang C, Mine Y. Multiple T cell epitope peptides suppress allergic responses in an egg allergy mouse model by the elicitation of forkhead box transcription factor 3- and transforming growth factor-beta-associated mechanisms. *Clin Exp Allergy*. 2010;40(4):668-78. Epub 2010/01/20.
69. Rupa P, Mine Y. Oral immunotherapy with immunodominant T-cell epitope peptides alleviates allergic reactions in a Balb/c mouse model of egg allergy. *Allergy*. 2012;67(1):74-82. Epub 2011/09/29.
70. Prickett SR, Voskamp AL, Dacumos-Hill A, Symons K, Rolland JM, O'Hehir RE. Ara h 2 peptides containing dominant CD4+ T-cell epitopes: candidates for a peanut allergy therapeutic. *J Allergy Clin Immunol*. 2011;127(3):608-15 e1-5. Epub 2010/11/26.