



Food allergy: epidemiology, pathogenesis, diagnosis, prevention, and treatment

Joao Pedro Lopes and Scott Sicherer

Food allergy affects up to 10% of the population. The identification of modifiable risk factors including skin barrier dysfunction, vitamin D deficiency, microbiome, and route and timing of allergen exposure is leading to effective prevention strategies, and some of which are now included in public health guidelines. An increasing understanding of the pathophysiology has improved diagnostic options and revealed novel manifestations such as delayed anaphylaxis to mammalian meat related to sensitization to a sugar moiety triggered by tick bites. Current diagnosis has improved with the commercialization of allergen component testing, and the diagnostics pipeline shows imminent advances for predicting reactivity, threshold and severity. The first FDA-approved food allergy therapy has come to fruition with superb additional approaches under investigation.

Address

Jaffe Food Allergy Institute, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Corresponding author: Sicherer, Scott (scott.sicherer@mssm.edu)

Current Opinion in Immunology 2020, 66:57–64

This review comes from a themed issue on **Allergy and hypersensitivity**

Edited by **Michael E Wechsler** and **Wanda Phipatanakul**

<https://doi.org/10.1016/j.coi.2020.03.014>

0952-7915/© 2020 Elsevier Ltd. All rights reserved.

Introduction

Food allergy is a common disorder, with an increasing prevalence [1]. Over the past few decades, there has been a rapid accumulation of knowledge on the epidemiology, natural course, pathogenesis, diagnosis, and management/treatment of food allergy. The past several years have witnessed an explosion in discovery, with practical translation to clinical interventions that are improving the lives of those affected and preventing new cases. The current review highlights some of the most recent findings and advances in food allergy, with particular emphasis on the new developments in prevention and treatment that supersede the traditionally recommended avoidance of allergens and management of allergic reactions after accidental exposure.

Epidemiology and natural history

Estimates of food allergy prevalence rates vary by age, geographic location, and study methodologies, but a general conclusion is that the disease is common, and the prevalence has been increasing [1]. Some estimates suggest that up to 10% of some populations are affected [1,2,3*,4]. The most common food allergens are peanut, tree nuts, cow's milk, hen's egg, fish, shellfish, wheat, soy, and seeds [1,2].

The identification of risk factors for food allergy may inform prevention and treatment approaches. Studies have identified dietary, environmental, genetic [5,6], and combinations of factors [1,7], including epigenetic mechanisms [8,9]. Some risk factors are modifiable [1,7], such as skin barrier dysfunction [10–12], vitamin D insufficiency, microbiome [12–14], route and timing of first exposure to the foods [11], maternal dietary habits [15], absence of early exposure to particular environmental allergens [10], while others [5,10], such as male gender, racial background or family history, are underlying non-modifiable risks [1].

The natural course of food allergy is variable for different foods/food groups. For example, resolution of peanut (around 20% for 4-year-olds), tree nuts (about 10%), fish, shellfish and seeds is less common than it is for egg, milk, wheat, and soy that show resolution rates of 45–50% or higher by age 5–10 years old, with continued resolution into adulthood [1,16]. For foods such as hen's egg and cow's milk, there are data supporting the ingestion of baked egg [17] and baked milk [18] as a factor contributing to a faster resolution of egg and milk allergy, respectively. It is interesting to note that adult-onset food allergy to milk, egg, wheat, and soy is reported by over 20% (per food) of adults with food allergy, indicating that these classically pediatric allergies that typically resolve are emerging in adults [3*].

Pathogenesis and mechanisms

Food allergy is a result of immune dysregulation and an abrogation of normal oral tolerance. Elucidating the mechanisms that lead to food allergy or tolerance is a significant research priority [12,19]. Normally, the antigens present in the food are presented to CD103+ dendritic cells (DC) in the gastrointestinal tract and after these cells migrate to regional lymph nodes, they promote immune tolerance, in part by the induction of T regulatory cells (Tregs) [20]. In food allergy, Th2-type responses characterize the immune response.

For example, interleukin-4 (IL-4), produced by several cell types, including basophils, natural killer T cells, and innate lymphoid cells, drive responses [19,21]. Skin basophils, in mouse models of atopic dermatitis, participate in sensitization to food allergens through the skin, leading, through IL-4, to IgE-mediated hypersensitivity [21]. The loss of integrity of the skin barrier, commonly present in patients with atopic dermatitis, is now understood as a mechanism to develop food allergy through environmental exposure, particularly when oral exposure is insufficient. This 'dual allergen exposure hypothesis,' initially proposed by Lack may explain the high rates of food allergy in children with atopic dermatitis, especially if they are not ingesting the food allergens early in life [12,19,20,22].

The study of the microbiome in the development of immune tolerance or food allergy has also been the subject of intense research, as it is thought that microbial interaction with the immune system may have an important role in immune tolerance and antigen sensitization [14,23,24]. Specific signatures of bacterial intestinal colonization have been identified in patients with food sensitization and food allergy [25*,26], with the changes in the microbiome appearing to precede the development of food allergy [27].

Diagnosis

The diagnosis of food allergy relies most heavily on the clinical history to determine whether the symptoms are related to allergy or other mechanisms and to identify culprit foods, while tests such as skin prick tests (SPT) and serum food-specific IgE measurements (sIgE) provide additional diagnostic information [1,28]. Skin and serum tests are very sensitive but not very specific and the most accurate test is the oral food challenge (OFC), a procedure that unfortunately carries concerns of triggering severe allergic reactions [29].

Tests such as SPT and sIgE are not relevant for disorders that are not mediated primarily by IgE, such as food protein-induced enterocolitis syndrome (FPIES). FPIES is characterized by repetitive delayed vomiting, with progression in many cases to dehydration and lethargy [30]. Eosinophilic esophagitis (EoE) [31] is an inflammatory condition presenting with dysphagia and associated with eosinophilic inflammation in the esophagus. The diagnosis is suspected when there is difficulty in swallowing specific foods that are bulkier, such as steak. The disorder is not typically diagnosed by SPT or sIgE as foods such as milk or wheat may trigger the inflammation despite negative tests. An interesting emerging allergy regards IgE responses to alpha-gal, a sugar moiety in mammalian meat [32**], with the clinical manifestation of allergic reactions starting several hours after ingestion of the culprit food and related to initial allergic sensitization to antigens from tick bites.

The cross-reactivity of food allergens with environmental allergens (pollens, cockroach, dust mite) may confound the interpretation of SPT and sIgE because the tests will detect proteins that do not typically trigger systemic reactions [1,33]. A major advance is the emerging use of component-resolved diagnostics (CRD) that can potentially refine the interpretation of SPT and sIgE that use multi-protein extracts because CRD measures responses to individual proteins, although clear cutoff values for those components are not yet available [34]. Another emerging test is the basophil activation test (BAT), which has shown excellent sensitivity and specificity and may add to diagnostic utility but is not yet commercialized [28,35]. Additional next generation tests that may help improve prediction of allergy, threshold, and severity include evaluation of IgE epitope binding, affinity [36,37], histamine release assay [38], mast cell activation test (MAT) [39], transcriptomics, epigenomics, and other biomarkers [40*,41,42]. The attempt to create predictive models and algorithms, using data from several of the above also show promise [43]. Table 1 summarizes some of the potential future diagnostic tests.

Prevention

Major advances in research about prevention of food allergy have resulted in worldwide changes in feeding recommendations [44]. The milestone Learning Early About Peanut (LEAP) study in 2015 showed early dietary introduction of peanut in infants with severe eczema, egg allergy, or both, resulted in a 70% (in patients with initial positive SPT) and 86% (in patients with negative initial SPT) reduction in peanut allergy 60 months later [45], promoting recommendations for the early dietary introduction of peanut in high-risk infants [46]. Prior notions and recommendations that high-risk families should delay introduction of allergens have been supplanted by recommendations to introduce peanut early in infants showing signs of allergy, and not treating common allergens any differently than other foods when deciding upon solid food introduction for infants in general [44].

Additional avenues of prevention besides early introduction are being evaluated, including alterations of the maternal diet, altering the microbiome, vaginal seeding of infants born by caesarian section (ongoing trial - [ClinicalTrials.gov](https://www.clinicaltrials.gov/ct2/show/study?term=NCT03567707) registration NCT03567707), early use of treatments to improve the skin barrier function and others [44]. The PEBBLES study is an ongoing phase 3 randomized controlled trial in 760 infants with family history of atopy, to assess the impact on food allergy and atopic dermatitis of the application of skin emollient twice a day during the first year of life [47], with a recently published study not showing evidence of an impact of daily emollient in the prevention of eczema at two-years of age in a similar population [48].

Table 1

Examples of future food allergy diagnostic tests

Test	Concept	Advantages	Disadvantages/limitations
BAT (basophil activation test) [28,35,42]	Flow cytometry-based assay measuring cell surface expression of CD63 (and CD203c) on exposure to allergen	- High specificity and sensitivity, which may allow BAT to substitute for OFC in some patients (especially useful to test for high doses of allergen) - Only 1 mL of peripheral blood required - Safe - Antihistamines do not interfere with test outcome	- considerable portion of patients (up to 10%) may be BAT non-responders, due to 'basophil anergy' - Requires specialized training and not scaled to commercial settings yet - Needs to be performed within 24 hours of collection (ideally within 4 hours) - Needs validation in large cohorts
Histamine release assay [38,42]	Whole blood incubated with allergen extract or anti-IgE, promoting release of histamine, that is quantified through fluorometry; can also be performed with patient serum (passive HR assay)	- If done with serum, may allow the use of stored samples, reducing time-sensitivity and the need for fresh blood samples	- Less sensitivity than BAT - Passive HR assay may have clinical use to confirm allergy, but high rate of false negatives, so less useful to rule out allergy - Needs validation in large cohorts
MAT (mast cell activation test) [39,42]	Test uses cultured human mast cells obtained from blood c-kit + CD34+ precursor myeloblasts, that are mixed with allergic patient's serum, with measurement of cell surface expression of CD63 (and CD107a) and function (prostaglandin D2 and beta-hexosaminidase release) on exposure to allergen	- Diagnostic performance may be superior to test modalities such as CRD and BAT - Serum samples from patients can be frozen and analyzed in batches, not time-sensitive like BAT - Patterns of response may have a correlation with severity of the reaction to the particular allergen - Mast cells are the main effector cells in allergic reactions (basophils have unclear role as effector cells)	- More time-consuming than BAT, due to the need to culture and differentiate human mast cells - Requires specialized training, particularly in the differentiation of human mast cells from donor peripheral blood myeloblasts - Needs validation in large cohorts
IgE epitope mapping [36,37,42]	Peptide microarray immunoassay performing large-scale IgE epitope mapping for food allergens (may be refined by measuring epitope antibody affinity)	- May improve ability to predict clinical reactivity, severity and tolerance - May be useful for clinical diagnosis but also add data regarding prognosis	- Positive allergen IgE binding shows sensitization but does not equal <i>in vivo</i> cross-link of IgE to mast cells or basophils - Needs validation in large cohorts
Transcriptomics/epigenomics [40]	Analysis of whole blood transcriptome and T-cell epigenome profiles to identify patterns of molecular signature associated with severity of reaction	- May allow to identify molecular signatures associated with severity of reaction to a particular allergen - The identification of molecular signatures may also have an impact in the future to predict which therapy could have the most impact in the treatment of a particular individual	- Needs specialized center and analysis in a center with robust tools for transcriptome and epigenome analysis - Needs validation in large cohorts

Treatment

Until recently, the management of food allergy has been strict allergen avoidance and prompt reactive treatment with emergency medications in the event of an allergic

reaction [1,49]. Remarkably, the first (January 2020) FDA approved treatment, a peanut oral immunotherapy (OIT) product, was approved for the mitigation of allergic reactions in children ages 4 to 17-years-old [50].

Table 2

Examples of future therapies for food allergy

Therapy	Concept	Comments
Allergen-specific [62–65]		
Alum-adsorbed immunotherapy [63]	SCIT with chemically modified, aluminum hydroxide adsorbed-allergen, with the goal of increasing tolerance to allergen	- Pilot study for peanut reporting safe and well tolerated therapy - Early studies for fish (NCT02382718) and peanut (NCT02991885) are ongoing
Vaccines [63,64]	- Intramuscular/Intradermal LAMP-DNA vaccine: allergen DNA combined with LAMP (lysosome-associated DNA proteins) sequences and inserted into plasmid vector DNA; plasmid vector DNA processed by APCs with goal of acquiring tolerance to allergen - VLP: single peanut allergens coupled to virus-like particles to generate allergen-specific vaccines - PVX-108: synthetic peptides that represent T-cell epitopes for major peanut allergens, with goal of targeting T cells specific for allergen	- In murine models, reduction of allergic symptoms during peanut challenge and reduction of peanut sIgE were observed - Ongoing phase I clinical trial with multivalent peanut allergy LAMP-DNA vaccine (NCT03755713) - PVX-108 undergoing double-blind placebo-controlled randomized trials
Modified recombinant proteins [65]	Use modified allergens/peptides that lost allergenicity (IgE interaction properties), but maintain immunogenicity (T cell interaction), with the goal of inducing Th1 and Treg responses to the allergen	- Potential to be safer, due to reduced allergenicity - Phase I trial in humans with high rate of adverse events (including anaphylaxis)
TLR-9 agonists (CpG oligonucleotides) [62,63]	CpG oligonucleotides administered as adjuvant of allergen immunotherapy, in order to stimulate Th1 and Treg immune responses, by binding to TLR-9	- Shown in murine models of peanut allergy, with decreased anaphylactic reactions with immunotherapy - Th1 stimulation may have a potential side effect of autoimmunity
TLR-4 Agonists (MPL/GLA) [62,63]	MPL (LPS derived from <i>Salmonella</i>) and GLA (synthetic form) used as adjuvants of allergen immunotherapy, in order to stimulate Th1 and Treg responses, as both are TLR-4 agonists	- Lower rates of anaphylaxis in murine models - Phase I trials with peanut ongoing - Th1 stimulation may have a potential side effect of autoimmunity
Interferon-gamma [62,63]	Cytokine promoting Th1 responses and suppressing Th2 responses	- Potential to allow for faster buildups of allergen immunotherapy - Th1 stimulation may have a potential side effect of autoimmunity
Nanoparticles [62,63]	System that can be used to deliver allergens in a way that reduces degradation in the GI tract and increases uptake efficiency; nanoparticles containing allergen can be coated with CpG, to promote Th1/Treg responses	- Peanut CpG nanoparticle delivery was well tolerated in murine model and showed favorable cytokine signature - Only animal data for use in food allergy; need further studies and better definition of kinetics of particle release and delivery to avoid sudden release of large amounts of allergen
Allergen non-specific Biologics [62,63,66]	- Anti-IgE (Omalizumab): monoclonal antibody binds free serum IgE, reducing its ability to bind mast cell and basophil IgE receptors - Anti-IL-4Rα (Dupilumab): monoclonal antibody blocks IL4-Rα blocking the action of IL-4 and IL-13, cytokines involved in the promotion of Th2 responses - Anti-IL-33 (Etokimab): monoclonal antibody blocks IL-33, an upstream cytokine (alarmin) involved in the promotion of Th2 responses	- Omalizumab: prior studies with a different anti-IgE agent had shown significant increases in reaction threshold to peanut protein. Ongoing trials with omalizumab as monotherapy, adjunct to oral immunotherapy and comparison between the two modes and placebo (OUTMATCH phase 3 clinical trial Clinicaltrials.gov NCT03881696) - Dupilumab: ongoing phase 2 studies with dupilumab as monotherapy and as adjunct for oral immunotherapy in patients with peanut allergy - Etokimab: ongoing phase 2 studies with etokimab as monotherapy in patients with peanut allergy

Table 2 (Continued)

Therapy	Concept	Comments
Chinese Traditional Medicine [66]	A Chinese herbal formula – Food Allergy Herbal Formula-2 (FAHF-2) has shown to decrease Th2 responses and to reduce IgE-mediated mast cell degranulation	- Phase 1 clinical trials showed it as safe and well tolerated - Clinical trials done as monotherapy and ongoing phase 2 trials as an adjunct for oral immunotherapy in patients with multiple food allergies
Probiotics [62,63,66]	As gut microbiome dysbiosis has been linked as a possible factor in the pathogenesis of food allergy, probiotics have been proposed as a potential therapy in the induction of immune tolerance	- Probiotics have been studied as adjuvants for peanut OIT, with initial trials showing high levels of desensitization and sustained unresponsiveness at 4-year follow-up, when compared to placebo

Indeed, OIT has been the most studied food allergy treatment approach [51]. For peanut OIT, after a phase 2 study showing an acceptable safety profile [52], the product underwent a phase 3 study with 551 participants between 4 and 17 years of age. The results showed 67.2% of the patients in the treatment group were able to tolerate a dose of 600 mg of peanut at the study exit food challenge, compared with 4.0% of the patients in the placebo group [53•]. Although the product was approved, it is being highly regulated because, on average, those under therapy experienced more allergic reactions and anaphylaxis than those on placebo with both groups instructed on peanut avoidance (aside from the doses taken). A systematic review and meta-analysis of peanut OIT [54•] that included 12 trials, showed an increased anaphylaxis risk of 3.12 (risk ratio; 95% confidence interval [CI] 1.76–5.5); number needed to treat to harm 7 (3–19) both during the build-up and the maintenance phases of the protocols. Given a trade-off of increased reactions versus a higher threshold of reactivity, this therapy (and others in the pipeline) requires an extensive shared decision-making effort between the medical provider and patient/family, to identify the best candidates for the currently approved treatment. The long-term benefits of OIT are also uncertain. A phase 2 study following peanut OIT subjects over three years and altering dosing regimens over time, suggested that patients under OIT maintained their level of desensitization, but that stopping the treatment or lowering the daily dose is associated with a recurrence of previous thresholds of clinical reactivity to the allergen [55]. Long-term adverse events are also still under further research, with current data suggesting a possible increased rate of EoE in patients undergoing OIT [56], and that risk seems to be also present in patients on sublingual immunotherapy (SLIT, another approach being studied) both for food and aeroallergens [57]. Of note, history of EoE is one of the package insert-listed contraindications for the approved peanut OIT product [50].

Epicutaneous immunotherapy (EPIT) is another approach that has been studied for desensitization. A phase 3 trial was published in 2019, on 356 peanut-allergic

patients, ages ranging from 4 to 11 years old, treated daily for 12 months with a peanut patch versus placebo, with 35.3% responders in the treatment group versus 13.6% in the placebo group [58•]. Although EPIT trials show a favorable side effect profile, mild localized symptoms in the area of administration (erythema, pruritus, swelling) are relatively common [59]. Overall, and pending additional data and larger studies, data suggest that OIT may have a more robust therapeutic effect than EPIT, but with a greater risk of adverse events, though the direct comparison of the two approaches is unlikely to be studied for some time.

With FDA approval of therapies that are not curative, continued allergen avoidance and readiness to recognize and treat allergic reactions is imperative. Advice about the day-to-day management of food allergy continues to be a crucial part of the treatment of patients and families. Clinical management includes counseling on issues such as ingredient labeling, allergic symptom recognition and threshold changes with eliciting factors such as exercise, alcohol use or acute illness and many other topics. Most patients and families experience anxiety related to food allergy, but there is a lack of dedicated mental health support, even at the majority of referral centers [60]. Some widespread issues, such as suffering bullying at school, which happens in 35–45% of children with food allergy, are not frequently addressed, as shown in a recent survey of allergists, with significant room for improvement in this and other areas [61].

Future therapies

In addition to OIT, EPIT, and SLIT, other allergen-specific approaches are being evaluated [62,63], including chemically modified aluminum-hydroxide adsorbed allergens, vaccines (DNA, virus-like particles, PVX-108) [64] and modified proteins [65].

Other adjuvants and adjunctive therapies [62,63] include Toll-Like Receptor (TLR) agonists (such as CpG oligonucleotides – TLR-9 – or monophosphoryl lipid A (MPL) and glucopyranosyl lipid A (GLA) – both TLR-4 agonists), cytokines (interferon- γ), and nanoparticles, a

delivery system with the potential of improving delivery and uptake of the allergens, as well as drugs or other adjunctive therapies such as CpG oligonucleotides [62,63].

Approaches that are not allergen-specific [62,63,66] include biologics currently approved for other atopic disorders, such as asthma and atopic dermatitis, such as omalizumab (anti-IgE) and dupilumab (IL-4R α blocker, blocking IL-4 and IL-13 pathways) among other prospects. These biologic agents have the potential to be used in an isolated fashion, with the goal of increasing the threshold dose for an allergic reaction (which theoretically may be particularly useful for patients with multiple allergies), but also the potential to be used as adjuvants during immunotherapy protocols, in an attempt to reduce the side effects of immunotherapy, particularly during the initial build-up phase, and those concepts are in the basis of several ongoing clinical trials (Table 2). Chinese herbal medicines and probiotics are other potential therapeutic tools that have been investigated.

Conclusions

The increasing prevalence of food allergy is worrisome, with all the impact this has on the patients and their families, but it is matched by relentless and exciting advances on the different areas of the study of food allergy, from a better understanding of its pathogenic mechanisms, to better and further refined diagnostic tools, meaningful approaches to prevention and to new treatment that open the door to a future where the hope is to move from an isolated recommendation of allergen avoidance to a possibility of treatment.

Conflict of interest statement

Nothing declared.

Acknowledgements

Scott H. Sicherer reports royalty payments from UpToDate and from Johns Hopkins University Press; grants to his institution from the National Institute of Allergy and Infectious Diseases, from Food Allergy Research and Education, and from HAL Allergy; and personal fees from the American Academy of Allergy, Asthma and Immunology as Deputy Editor of the Journal of Allergy and Clinical Immunology: In Practice, outside of the submitted work.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Sicherer SH, Sampson HA: **Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management.** *J Allergy Clin Immunol* 2018, **141**:41-58.
2. Dunlop JH, Keet CA: **Epidemiology of food allergy.** *Immunol Allergy Clin North Am* 2018, **38**:13-25.
3. Gupta RS, Warren CM, Smith BM, Jiang J, Blumenstock JA, Davis MM, Schleimer RP, Nadeau KC: **Prevalence and severity of food allergies among US adults.** *JAMA Netw Open* 2019, **2**: e185630.
4. Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang J, Davis MM, Nadeau KC: **The public health impact of parent-reported childhood food allergies in the United States.** *Pediatrics* 2018, **142**.
5. Asai Y, Eslami A, van Ginkel CD, Akhbar L, Wan M, Yin D, Ellis G, Ben-Shoshan M, Marenholz I, Martino D *et al.*: **A Canadian genome-wide association study and meta-analysis confirm HLA as a risk factor for peanut allergy independent of asthma.** *J Allergy Clin Immunol* 2018, **141**:1513-1516.
6. Asai Y, Eslami A, van Ginkel CD, Akhbar L, Wan M, Ellis G, Ben-Shoshan M, Martino D, Ferreira MA, Allen K *et al.*: **Genome-wide association study and meta-analysis in multiple populations identifies new loci for peanut allergy and establishes C11orf/EMSY as a genetic risk factor for food allergy.** *J Allergy Clin Immunol* 2018, **141**:991-1001.
7. Yu JE, Mallapaty A, Miller RL: **It's not just the food you eat: environmental factors in the development of food allergies.** *Environ Res* 2018, **165**:118-124.
8. D'Argenio V, Del Monaco V, Paparo L, De Palma FDE, Nocerino R, D'Alessio F, Visconte F, Discepolo V, Del Vecchio L, Salvatore F *et al.*: **Altered miR-193a-5p expression in children with cow's milk allergy.** *Allergy* 2018, **73**:379-386.
9. Mondoulet L, Dioszeghy V, Busato F, Plaquet C, Dhelft V, Bethune K, Leclerc L, Daviaud C, Ligouis M, Sampson H *et al.*: **Gata3 hypermethylation and Foxp3 hypomethylation are associated with sustained protection and bystander effect following epicutaneous immunotherapy in peanut-sensitized mice.** *Allergy* 2019, **74**:152-164.
10. Sasaki M, Peters RL, Koplin JJ, Field MJ, McWilliam V, Sawyer SM, Vuillermin PJ, Pezic A, Gurrin LC, Douglass JA *et al.*: **Risk factors for food allergy in early adolescence: the SchoolNuts study.** *J Allergy Clin Immunol Pract* 2018, **6**:496-505.
11. Grimshaw KEC, Roberts G, Selby A, Reich A, Butiene I, Clausen M, Dubakiene R, Fianor A, Flocchi A, Grabenhenrich LB *et al.*: **Risk factors for hen's egg allergy in Europe: EuroPrevall birth cohort.** *J Allergy Clin Immunol Pract* 2020, **8**:1341-1348.e5 <http://dx.doi.org/10.1016/j.jaip.2019.11.040> Epub 2019 Dec 14.
12. Berin MC: **Pathogenesis of IgE-mediated food allergy.** *Clin Exp Allergy* 2015, **45**:1483-1496.
13. Hussain M, Bonilla-Rosso G, Kwong Chung CKC, Bariswyl L, Rodriguez MP, Kim BS, Engel P, Noti M: **High dietary fat intake induces a microbiota signature that promotes food allergy.** *J Allergy Clin Immunol* 2019, **144**:157-170 e158.
14. Bunyavanich S, Berin MC: **Food allergy and the microbiome: current understandings and future directions.** *J Allergy Clin Immunol* 2019, **144**:1468-1477.
15. Kim YH, Kim KW, Lee SY, Koo KO, Kwon SO, Seo JH, Suh DI, Shin YH, Ahn K, Oh SY *et al.*: **Maternal perinatal dietary patterns affect food allergy development in susceptible infants.** *J Allergy Clin Immunol Pract* 2019, **7**:2337-2347 e2337.
16. Savage J, Sicherer S, Wood R: **The natural history of food allergy.** *J Allergy Clin Immunol Pract* 2016, **4**:196-203 quiz 204.
17. Peters RL, Dharmage SC, Gurrin LC, Koplin JJ, Ponsonby AL, Lowe AJ, Tang ML, Tey D, Robinson M, Hill D *et al.*: **The natural history and clinical predictors of egg allergy in the first 2 years of life: a prospective, population-based cohort study.** *J Allergy Clin Immunol* 2014, **133**:485-491.
18. Kim JS, Nowak-Wegrzyn A, Sicherer SH, Noone S, Moshier EL, Sampson HA: **Dietary baked milk accelerates the resolution of cow's milk allergy in children.** *J Allergy Clin Immunol* 2011, **128**:125-131 e122.
19. Sampson HA, O'Mahony L, Burks AW, Plaut M, Lack G, Akdis CA: **Mechanisms of food allergy.** *J Allergy Clin Immunol* 2018, **141**:11-19.

20. Tordesillas L, Berin MC, Sampson HA: **Immunology of food allergy.** *Immunity* 2017, **47**:32-50.
21. Hussain M, Borcard L, Walsh KP, Pena Rodriguez M, Mueller C, Kim BS, Kubo M, Artis D, Noti M: **Basophil-derived IL-4 promotes epicutaneous antigen sensitization concomitant with the development of food allergy.** *J Allergy Clin Immunol* 2018, **141**:223-234 e225.
22. Lack G: **Update on risk factors for food allergy.** *J Allergy Clin Immunol* 2012, **129**:1187-1197.
23. Ho HE, Bunyavanich S: **Role of the microbiome in food allergy.** *Curr Allergy Asthma Rep* 2018, **18**:27.
24. Kemter AM, Nagler CR: **Influences on allergic mechanisms through gut, lung, and skin microbiome exposures.** *J Clin Invest* 2019, **130**:1483-1492.
25. Savage JH, Lee-Sarwar KA, Sordillo J, Bunyavanich S, Zhou Y, O'Connor G, Sandel M, Bacharier LB, Zeiger R, Sodergren E *et al.*: **A prospective microbiome-wide association study of food sensitization and food allergy in early childhood.** *Allergy* 2018, **73**:145-152.
- This paper investigates the role of the microbiome in the development of food allergy. The authors analyze intestinal microbiome from children aged 3-6 months and later, at 3-years-old, assess, in the same children, sensitization to different foods and reports of allergic reactions to those foods. A temporal association is identified between bacterial colonization and food sensitization/allergy, suggesting the microbiome has a causal role in the development of food allergy.
26. Fazlollahi M, Chun Y, Grishin A, Wood RA, Burks AW, Dawson P, Jones SM, Leung DYM, Sampson HA, Sicherer SH *et al.*: **Early-life gut microbiome and egg allergy.** *Allergy* 2018, **73**:1515-1524.
27. Azad MB, Konya T, Guttman DS, Field CJ, Sears MR, HayGlass KT, Mandhane PJ, Turvey SE, Subbarao P, Becker AB *et al.*: **Infant gut microbiota and food sensitization: associations in the first year of life.** *Clin Exp Allergy* 2015, **45**:632-643.
28. Anotegui IJ, Melioli G, Canonica GW, Caraballo L, Villa E, Ebisawa M, Passalacqua G, Savi E, Ebo D, Gomez RM *et al.*: **IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper.** *World Allergy Organ J* 2020, **13**:100080.
29. Bird JA, Leonard S, Groetch M, Assa'ad A, Cianferoni A, Clark A, Crain M, Fausnight T, Fleischer D, Green T *et al.*: **Conducting an oral food challenge: an update to the 2009 adverse reactions to Foods Committee Work Group Report.** *J Allergy Clin Immunol Pract* 2020, **8**:75-90 e17.
30. Nowak-Wegrzyn A, Chehade M, Groetch ME, Spergel JM, Wood RA, Allen K, Atkins D, Bahna S, Barad AV, Berin C *et al.*: **International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: executive summary-workgroup report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology.** *J Allergy Clin Immunol* 2017, **139**:1111-1126 e1114.
31. Chehade M, Jones SM, Pesek RD, Burks AW, Vickery BP, Wood RA, Leung DYM, Furuta GT, Fleischer DM, Henning AK *et al.*: **Phenotypic characterization of eosinophilic esophagitis in a large multicenter patient population from the consortium for food allergy research.** *J Allergy Clin Immunol Pract* 2018, **6**:1534-1544 e1535.
32. Platts-Mills TAE, Commins SP, Biedermann T, van Hage M, Levin M, Beck LA, Diuk-Wasser M, Jappe U, Apostolovic D, Minnicozzi M *et al.*: **On the cause and consequences of IgE to galactose-alpha-1,3-galactose: a report from the National Institute of Allergy and Infectious Disease workshop on understanding IgE-mediated mammalian meat allergy.** *J Allergy Clin Immunol* 2020, **145**:1061-1071 <http://dx.doi.org/10.1016/j.jaci.2020.01.047> Epub 2020 Feb 10.
- This paper summarizes the discussions of a 2018 National Institute of Allergy and Infectious Diseases workshop on alpha-gal syndrome that involved international experts in the area. The paper reviews all the current knowledge on the syndrome, discussed at the background, defining a base for future research in the area.
33. Sicherer SH: **Clinical implications of cross-reactive food allergens.** *J Allergy Clin Immunol* 2001, **108**:881-890.
34. Flores Kim J, McCleary N, Nwaru BI, Stoddart A, Sheikh A: **Diagnostic accuracy, risk assessment, and cost-effectiveness of component-resolved diagnostics for food allergy: a systematic review.** *Allergy* 2018, **73**:1609-1621.
35. Song Y, Wang J, Leung N, Wang LX, Lisann L, Sicherer SH, Scurlock AM, Pesek R, Perry TT, Jones SM *et al.*: **Correlations between basophil activation, allergen-specific IgE with outcome and severity of oral food challenges.** *Ann Allergy Asthma Immunol* 2015, **114**:319-326.
36. Lin J, Sampson HA: **IgE epitope mapping using peptide microarray immunoassay.** *Methods Mol Biol* 2017, **1592**:177-187.
37. Suarez-Farinas M, Suprun M, Chang HL, Gimenez G, Grishina G, Getts R, Nadeau K, Wood RA, Sampson HA: **Predicting development of sustained unresponsiveness to milk oral immunotherapy using epitope-specific antibody binding profiles.** *J Allergy Clin Immunol* 2019, **143**:1038-1046.
38. Larsen LF, Juel-Berg N, Hansen KS, Clare Mills EN, van Ree R, Poulsen LK, Jensen BM: **A comparative study on basophil activation test, histamine release assay, and passive sensitization histamine release assay in the diagnosis of peanut allergy.** *Allergy* 2018, **73**:137-144.
39. Bahri R, Custovic A, Korosec P, Tsoumani M, Barron M, Wu J, Sayers R, Weimann A, Ruiz-Garcia M, Patel N *et al.*: **Mast cell activation test in the diagnosis of allergic disease and anaphylaxis.** *J Allergy Clin Immunol* 2018, **142**:485-496 e416.
40. Do AN, Watson CT, Cohain AT, Griffin RS, Grishin A, Wood RA, Wesley Burks A, Jones SM, Scurlock A, Leung DYM *et al.*: **Dual transcriptomic and epigenomic study of reaction severity in peanut-allergic children.** *J Allergy Clin Immunol* 2020, **145**:1219-1230 <http://dx.doi.org/10.1016/j.jaci.2019.10.040> Epub 2019 Dec 12.
- This paper expands the mechanistic understanding of severity of reaction in peanut allergy, through studying the transcriptome and epigenome of peanut-allergic children at the time of *in vivo* reactions. The authors identify variable expression of 318 genes and differential DNA methylation of 203 CpG sites during the reaction that are associated with the severity of reaction.
41. Krogulska A, Wood RA: **Peanut allergy diagnosis: moving from basic to more elegant testing.** *Pediatr Allergy Immunol* 2020, **31**:346-357 <http://dx.doi.org/10.1111/pai.13215> Epub 2020 Feb 11.
42. Koplin JJ, Perrett KP, Sampson HA: **Diagnosing peanut allergy with fewer oral food challenges.** *J Allergy Clin Immunol Pract* 2020, **31**:346-357.
43. Chinthrajah RS, Purington N, Andorf S, Rosa JS, Mukai K, Hamilton R, Smith BM, Gupta R, Galli SJ, Desai M *et al.*: **Development of a tool predicting severity of allergic reaction during peanut challenge.** *Ann Allergy Asthma Immunol* 2018, **121**:69-76 e62.
44. Perkin MR, Togias A, Koplin J, Sicherer S: **Food allergy prevention: more than peanut.** *J Allergy Clin Immunol Pract* 2020, **8**:1-13.
45. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, Brough HA, Phippard D, Basting M, Feeney M *et al.*: **Randomized trial of peanut consumption in infants at risk for peanut allergy.** *N Engl J Med* 2015, **372**:803-813.
46. Togias A, Cooper SF, Acebal ML, Assa'ad A, Baker JR Jr, Beck LA, Block J, Byrd-Bredbenner C, Chan ES, Eichenfield LF *et al.*: **Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel.** *J Allergy Clin Immunol* 2017, **139**:29-44.
47. Lowe A, Su J, Tang M, Lodge CJ, Matheson M, Allen KJ, Varigos G, Sasi A, Cranswick N, Hamilton S *et al.*: **PEBBLES study protocol: a randomised controlled trial to prevent atopic dermatitis, food allergy and sensitisation in infants with a family history of allergic disease using a skin barrier improvement strategy.** *BMJ Open* 2019, **9**:e024594.

48. Chalmers JR, Haines RH, Bradshaw LE, Montgomery AA, Thomas KS, Brown SJ, Ridd MJ, Lawton S, Simpson EL, Cork MJ *et al.*: **Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial.** *Lancet* 2020, **395**:962-972 [http://dx.doi.org/10.1016/S0140-6736\(19\)32984-8](http://dx.doi.org/10.1016/S0140-6736(19)32984-8) Epub 2020 Feb 19.
 49. Oriel RC, Wang J: **Diagnosis and management of food allergy.** *Pediatr Clin North Am* 2019, **66**:941-954.
 50. Administration FaD: *Palforzia Prescribing Information*. 2020. [Accessed in February 2020].
 51. Wang J: **Advances in the management of peanut allergy (oral immunotherapy and epicutaneous immunotherapy).** *Allergy Asthma Proc* 2020, **41**:5-9.
 52. Bird JA, Spergel JM, Jones SM, Rachid R, Assa'ad AH, Wang J, Leonard SA, Laubach SS, Kim EH, Vickery BP *et al.*: **Efficacy and safety of AR101 in oral immunotherapy for peanut allergy: results of AR001, a randomized, double-blind, placebo-controlled phase 2 clinical trial.** *J Allergy Clin Immunol Pract* 2018, **6**:476-485 e473.
 53. Investigators PGoC, Vickery BP, Vereda A, Casale TB, Beyer K, du Toit G, Hourihane JO, Jones SM, Shreffler WG, Marcantonio A *et al.*: **AR101 oral immunotherapy for peanut allergy.** *N Engl J Med* 2018, **379**:1991-2001.
- This paper reports the results of a phase 3 randomized, double-blind, placebo-controlled clinical trial for oral immunotherapy for peanut allergy in 551 participants. The study reported 67.2% of those in the active treatment group versus 4.0% of those in the placebo group tolerated 600 mg or more of peanut protein at the exit food challenge. The results of this trial formed the basis of the first FDA-approved peanut allergy treatment.
54. Chu DK, Wood RA, French S, Fiocchi A, Jordana M, Waserman S, Brozek JL, Schunemann HJ: **Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety.** *Lancet* 2019, **393**:2222-2232.
- This paper is a systematic review and meta-analysis of the efficacy and safety outcomes of 12 peanut oral immunotherapy trials. The authors identify an increased risk of anaphylaxis in the treatment group versus no treatment, with a relative risk ratio of 3.12 (95% CI [1.76–5.55]). Patients on the oral immunotherapy group in the different trials were more likely to pass a supervised oral food challenge (risk ratio 12.42 (95% CI [6.82–22.61])). The study underscores the risk benefit issues in applying this approach.
55. Chinthrajah RS, Purington N, Andorf S, Long A, O'Laughlin KL, Lyu SC, Manohar M, Boyd SD, Tibshirani R, Maecker H *et al.*: **Sustained outcomes in oral immunotherapy for peanut allergy (POISED study): a large, randomised, double-blind, placebo-controlled, phase 2 study.** *Lancet* 2019, **394**:1437-1449.
 56. Petroni D, Spergel JM: **Eosinophilic esophagitis and symptoms possibly related to eosinophilic esophagitis in oral immunotherapy.** *Ann Allergy Asthma Immunol* 2018, **120**:237-240 e234.
 57. Cafone J, Capucilli P, Hill DA, Spergel JM: **Eosinophilic esophagitis during sublingual and oral allergen immunotherapy.** *Curr Opin Allergy Clin Immunol* 2019, **19**:350-357.
 58. Fleischer DM, Greenhawt M, Sussman G, Begin P, Nowak-Wegrzyn A, Petroni D, Beyer K, Brown-Whitehorn T, Hebert J, Hourihane JO *et al.*: **Effect of epicutaneous immunotherapy vs placebo on reaction to peanut protein ingestion among children with peanut allergy: the PEPITES randomized clinical trial.** *JAMA* 2019, **321**:946-955.
- This paper reports the results of a phase 3 randomized, double-blind, placebo-controlled clinical trial for epicutaneous immunotherapy for peanut allergy, in 356 participants. They found 35.4% in the peanut-patch treatment group versus 13.6% in the placebo group responded to the treatment goal of increasing eliciting dose of reaction to peanut protein.
59. Wang J, Sampson HA: **Safety and efficacy of epicutaneous immunotherapy for food allergy.** *Pediatr Allergy Immunol* 2018, **29**:341-349.
 60. Herbert LJ, Marchisotto MJ, Sharma H, Gupta R, Bilaver LA: **Availability of mental health services for patients with food allergy.** *J Allergy Clin Immunol Pract* 2019, **7**:2904-2905.
 61. Bingemann T, Herbert LJ, Young MC, Sicherer SH, Petty CR, Phipatanakul W, Bartnikas LM: **Deficits and opportunities in allergists' approaches to food allergy-related bullying.** *J Allergy Clin Immunol Pract* 2020, **8**:343-345 e342.
 62. Virkud YV, Wang J, Shreffler WG: **Enhancing the safety and efficacy of food allergy immunotherapy: a review of adjunctive therapies.** *Clin Rev Allergy Immunol* 2018, **55**:172-189.
 63. Nicolaides RE, Parrish CP, Bird JA: **Food allergy immunotherapy with adjuvants.** *Immunol Allergy Clin North Am* 2020, **40**:149-173.
 64. Storni F, Zeltins A, Balke I, Heath MD, Kramer MF, Skinner MA, Zha L, Roesti E, Engeroff P, Muri L *et al.*: **Vaccine against peanut allergy based on engineered virus-like particles displaying single major peanut allergens.** *J Allergy Clin Immunol* 2020, **145**:1240-1253.e3 <http://dx.doi.org/10.1016/j.jaci.2019.12.007> Epub 2019 Dec 19.
 65. Wood RA, Sicherer SH, Burks AW, Grishin A, Henning AK, Lindblad R, Stablein D, Sampson HA: **A phase 1 study of heat/phenol-killed, *E. coli*-encapsulated, recombinant modified peanut proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) for the treatment of peanut allergy.** *Allergy* 2013, **68**:803-808.
 66. Long A, Borro M, Sampath V, Chinthrajah RS: **New developments in non-allergen-specific therapy for the treatment of food allergy.** *Curr Allergy Asthma Rep* 2020, **20**:3.