Food Allergies: The Basics

By Kathryn Holland

Word Count: 1,683

Table of Contents:

What are Food Allergies?

Food allergies are immune reactions to proteins of specific food. They can be immunoglobulin E (IgE) mediated or non-IgE-mediated. Non-IgE-mediated allergies are inflammatory disorders of the gut, and can be either subacute or chronic. IgE-mediated food allergies, on the other hand, are more commonly recognized. They are characterized by the fast onset of symptoms after the ingestion of a food antigen (Zhang, et al.). Food allergens tend to be water-soluble glycoproteins resistant to breakdown. They are readily transported across the intestine's mucosal membrane. The immune system of patients with food allergy interpret the antigens in these foods as harmful substances. In response to exposure, IgE antibodies specific for the given food antigen are released. These bind to basophils, macrophages, mast cells, and dendritic cells. The release of these mediators induce the contraction of smooth muscle, vasodilation, and mucus secretion. Eosinophils and lymphocytes are activated by macrophages, which release cytokines along with mast cells (*Figure 1*). The result is prolonged inflammation in the skin, the respiratory tract, the gastrointestinal tract, and the cardiovascular system. If left untreated for long enough, an allergic reaction can result in anaphylaxis, which entails the constriction of airways, rapid but weak beating of the pulse, severe blood pressure drops, and loss of consciousness or even death.

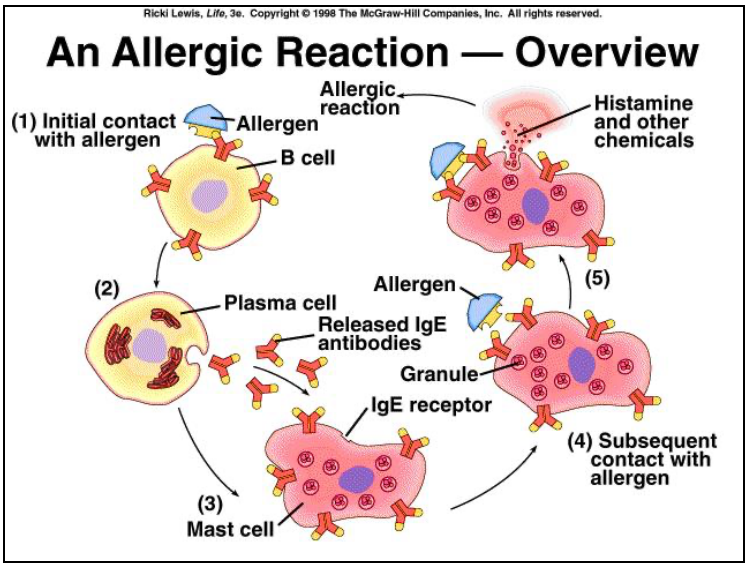

Fig 1. *When a food allergen enters the digestive system and the mucosal membrane, contact triggers B cells to differentiate into plasma cells, which release IgE-antibodies. These antibodies bind to white cells, such as the mast cell in the diagram, via IgE receptors. Subsequent contact with the allergen would trigger the white cells to release histamine and other chemicals, inducing inflammation in an allergic reaction.*

The following are other possible symptoms of an allergic reaction to food:

- Flushing – reddening of the face
- Angioedema – swelling of the body
- Urticaria – a skin reaction causing itchy welts; “Hives”
- Rhinorrhea – the dripping of mucus from the nose
- Sneezing
- Dyspnea – struggled breathing
- Laryngeal edema – abnormal accumulation of fluid in the tissues of the larynx
- Wheezing
- Nausea/vomiting

- Abdominal pain
- Diarrhea

(Lopez, et al.)

Over 170 foods are recognized as triggers for food allergy. Out of all food allergies, the most common ones include milk, eggs, fish, shellfish, tree nuts, peanuts, wheat, sesame, and soy (Canani, et al.). Some allergies such as milk, egg, wheat, or soy, usually recover within the first few years of life as the patient gains clinical tolerance. Others, such as those to peanuts and seafood, are more persistent, and tend to last for the rest of one's life (Lopez, et al.).

Diagnosis and Treatment

Diagnosing food allergy is frequently carried out via skin prick tests and allergy blood tests. In the skin-prick test, the skin is pricked with a lancet carrying the extract of an allergen. After fifteen minutes, if the site of the prick is raised and red, the person will be diagnosed with food allergy. An allergy blood test, on the other hand, measures the level of IgE antibodies in the bloodstream. Abnormal levels of IgE antibodies indicate an allergy to the specific food or protein. However, these tests do not always accurately diagnose a food allergy. Oftentimes, the test result may be a false positive, leading to unnecessary food restrictions being placed upon the patient, and potentially malnutrition, poor weight gain, and reduced quality of life. Getting false positives is especially common for individuals with atopic dermatitis, who can often have high total IgE levels irrespective of food allergy (*National Institute of Allergy and Infectious Diseases*). In order to prevent misdiagnosis, an National Institute of Allergy and Infectious Diseases (NIAID) clinical trial was begun in 2019 to identify threshold IgE levels to peanut and milk (or a component of these foods) that determine whether an individual has a food allergy. This would clarify the right time to perform an oral food challenge for a certain diagnosis. Those taking part in the trial have atopic dermatitis who may have high total IgE levels and allergy to

milk, peanuts, or both. The study is expected to go on until 2027 (*National Institute of Allergy and Infectious Diseases*).

Individuals diagnosed with food allergy must take extensive precautions when eating. Parents and children must be able to properly read food labels in case the item they would like to consume contains an allergen. Those at risk for anaphylaxis should carry epinephrine and antihistamines at all times, be trained to recognize the initial symptoms immediately, and learn how to self-administer auto-injectables (Lopez, et al.).

Theories as to Why Food Allergy Incidence has Increased

The precise reason for why there has been such a significant rise in food allergies remains unknown. Over the years, however, there have been many studies pointing to different hypotheses. One of the most well-known theories is the “Hygiene Hypothesis,” proposed by Dr. David Strachan in 1989. It states that there may be a link between the rise in allergic diseases and reduced microbial exposure due to measures implemented as a means of protecting against infection. The Hygiene Hypothesis has gone through many refinements, leading to the proposal of the “Old Friends Mechanism,” proposed by Graham Rook in 2003. This theorizes that instead of humans gaining vital microbial exposures through crowd infections (ie. colds, measles), that microbes have been present since primate evolution. These microbes include those inhabiting both indoor and outdoor environments, as well as commensal microbes acquired from skin, gut, and respiratory tract from other humans. They help shape the human microbiome, the community of microbiota in the body (Bloomfield et al.) (*Figure 2*).

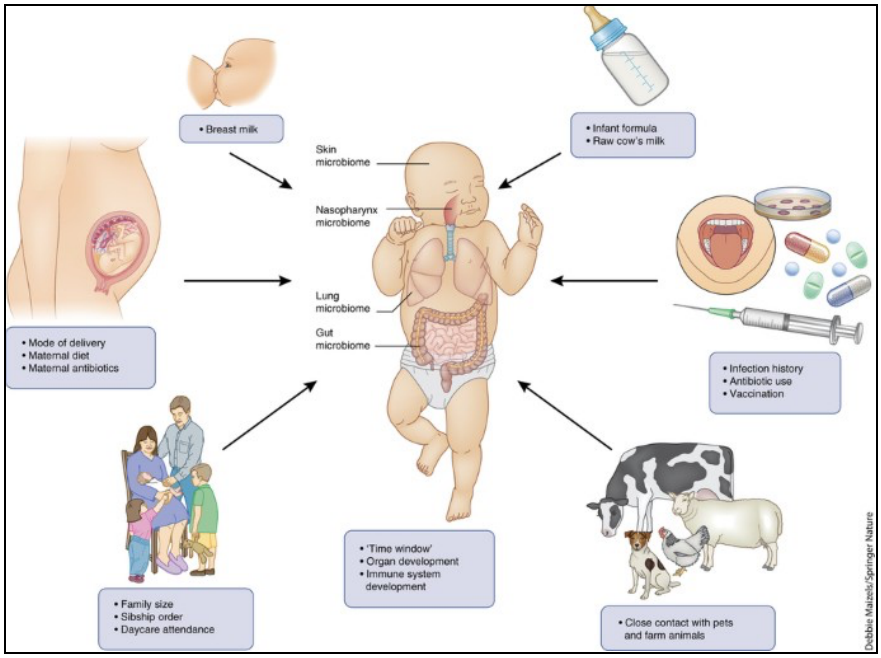

Fig 2. *The early stages of life are the most important when it comes to developing the immune system, and hence determining food allergy risk. Factors such as breast milk and consumption of antibiotics are key to shaping the microbiome, as these affect the type of microbiota that will prevail in the gut. Other factors such as mode of delivery and family size have previously been found to be related to the onset of allergy, but they do not share a causal relationship.*

In 2011, the “Biodiversity Hypothesis” was introduced. It states that contact with natural environments enriches the human microbiome. This in turn promotes immune balance. In the rapidly urbanizing world experiencing global warming, biodiversity is being lost, and this is said to be connected with the increase in inflammatory disorders, including allergies (Haahtela).

Accumulating evidence over the years has shown the Hygiene Hypothesis to be inaccurate, and epidemiological studies now confirm that childhood infections do not protect against allergic disorders (Bloomfield et al.). Research has instead provided more support for the Old Friends

Mechanism and the Biodiversity Hypothesis. The early stages of a newborn's life are the most impactful for the shaping of the immune system and the microbiome, particularly the microbiome of the gut (Haahtela).

Role of the Microbiome

The microbiome's composition affects the function, development, and differentiation of regulatory T (Treg) cells, which regulate adaptive immune responses. Recently, there has been increasing interest in how dysbiosis, or dysregulation of resident microbial communities, may be associated with allergy risk.

Many studies have directly measured microbial diversity and composition in subjects with and without food allergy, and they find that gut microbiota differs in subjects with food allergy (Bunyavanich, Berin). One study on 141 children either with or without egg allergy from the multi-center, US-based Consortium for Food Allergy Research, found that genera from *Lachnospiraceae*, *Streptococcaceae*, and *Leuconostocaceae* were differentially abundant in the gut microbiome of egg allergic children compared to the controls (Fazlollahi, et al.).

Another study examined 226 infants with milk allergy for 8 years, and found that taxa from the Firmicutes phylum were enriched in the gut microbiome of milk-allergic infants 3-6 months old. These infants' allergy resolved by the end of 8 years. These bacterial trends were not present in 3-6 month old infants who exhibited persistent milk allergy after 8 years, nor in infants at more than 6 months old (Bunyanich, et al.). The findings of this study and many more indicate that certain types of microbiota are associated with the development of food allergy, as well as further emphasize the importance of timing in the shaping of the microbiota.

There are also some species of bacteria which have been discovered to be protective against food allergy through the production of peripheral antigen-experienced regulatory T cells, particularly the strains of the *Clostridia* species (Bunyavanich, Berin). In some studies, *Clostridia* has been observed to be enriched in allergen-sensitized subjects, which may seem counter-intuitive (Han, et.al). However, many studies, such as one mice study on gnotobiotic mice from 2014, have found that *Clostridia* enrichment plays a role in regulating lymphoid cell function in the immune system as well as intestinal epithelial permeability (Stefka, et al.). Regulation of these actions may prevent food allergy.

Future Directions and Preventative Treatments

There is ongoing research on microbiome therapy, which may provide a means of food allergy prevention and treatment. One aspect of this entails the use of prebiotics. Prebiotics are typically high-fiber foods that act as food for the human microflora, aiming to improve the balance of microorganisms (Sestito, et al.). Regarding food allergy, there is evidence to suggest that consumption of prebiotics provides more favorable microbial colonization patterns. This could potentially prevent allergy through the acquisition of tolerance (Bunyavanich, Berin). Currently, there are limited studies on the role of prebiotic supplementation in food allergy prevention, and more research is needed to evaluate the benefits.

Another aspect of microbiome therapy involves probiotics, which are live organisms possessing health benefits when administered into the body (Sestito, et al.) (*Figure 3*).

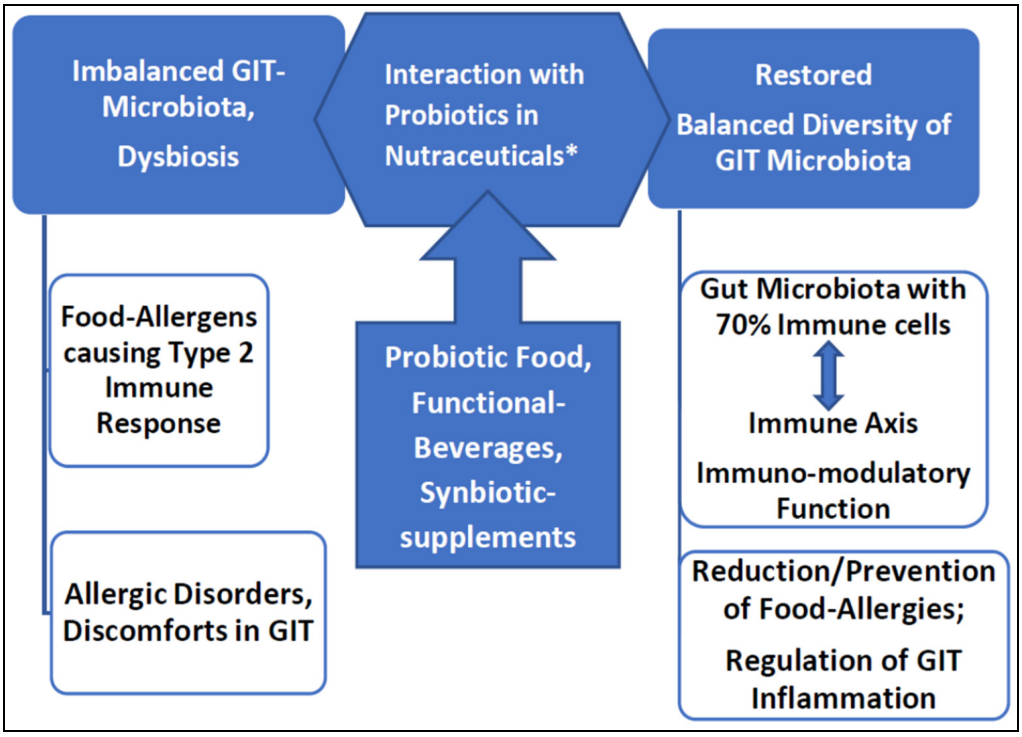

Fig 3. *Probiotics aim to restore balanced diversity in the microbiota of the gut. If an individual has a food allergic disorder, this may be because of the imbalance of the microbiome. Taking probiotics may therefore result in reduction or prevention of food allergies.*

There have been few clinical trials investigating the beneficial effects of probiotics on the development of food sensitization. However, when it comes to fully developed food allergy, research implies that probiotics may accelerate tolerance to foods. In a study on 55 infants with cow's milk allergy, either an extensively hydrolyzed casein formula (EHCF) or an EHCF supplemented with *Lactobacillus* GG (LGG) was given to the subjects. Those fed the EHCF supplemented with LGG exhibited augmented development of tolerance to cow's milk protein compared to the control group (Canani). There was another study looking at probiotics' effects on individuals with peanut allergy. Children with the allergy were given daily peanut oral immunotherapy (POIT), in addition to being given either a supplement of the probiotic

Lactobacillus rhamnosus CGMCC 1.3724 or with a placebo (control). The majority of those given POIT and the probiotic eventually became desensitized compared to those receiving POIT plus the placebo (Hsiao, et al.). There still needs to be further investigation into probiotics' role as a preventative or therapeutic agent for food allergies, and their use is currently only recommended for treatment of eczema.

New methods and approaches are being implemented in the field of the microbiome to better understand its role in food allergy. This involves analysis of diseased and healthy microbial populations to investigate commensal microbes and their influence on disease pathology, gut homeostasis, and immune response. There have been advances particularly in metabolomics, the study of metabolites in biofluids, tissues, or organisms. A method called untargeted metabolomic profiling has proved to be a powerful technique for dissecting altered pathways contributing to complex diseases. It is useful in that it reveals the genetic-environment-health relationship, as it can identify beneficial bacteria associated with a disease using their metabolomic "fingerprint." The bacteria can then be cultured and administered to the patient as treatment (Bunyavanich, Berin). The development of therapeutics for food allergy is still undergoing research, but areas such as targeted bacterial therapies so far look promising as treatments or preventatives.

Works Cited

Berni Canani, Roberto, et al. "Effect of Lactobacillus GG on Tolerance Acquisition in Infants with Cow's Milk Allergy: A randomized Trial." *Journal of Allergy and Clinical Immunology*, vol. 129, no. 2, Feb. 2012, p. 580-582.e5, https://doi.org/10.1016/j.jaci.2011.10.004.

---. "Gut Microbiome as Target for Innovative Strategies against Food Allergy." *Frontiers in Immunology*, vol. 10, 15 Feb. 2019, https://doi.org/10.3389/fimmu.2019.00191.

Bloomfield, Sally F., et al. "Time to Abandon the Hygiene Hypothesis: New Perspectives on Allergic Disease, the Human Microbiome, Infectious Disease Prevention and the Role of Targeted Hygiene." *Perspectives in Public Health*, vol. 136, no. 4, 27 June 2016, pp. 213-24, https://doi.org/10.1177/1757913916650225.

Bunyavanich, Supinda, and M. Cecilia Berin. "Food Allergy and the Microbiome: Current Understandings and Future Directions." *Journal of Allergy and Clinical Immunology*, vol. 144, no. 6, Dec. 2019, pp. 1468-77, https://doi.org/10.1016/j.jaci.2019.10.019.

Bunyavanich, Supinda, et al. "Early-life Gut Microbiome Composition and Milk Allergy Resolution." *Journal of Allergy and Clinical Immunology*, vol. 138, no. 4, Oct. 2016, pp. 1122-30, https://doi.org/10.1016/j.jaci.2016.03.041.

"Diagnosing Food Allergy." *National Institute of Allergy and Infectious Diseases*, www.niaid.nih.gov/diseases-conditions/diagnosing-food-allergy#:~:text=The%20most%20frequently%20used%20food,prick%20after%20about%2015%20minutes. Accessed 14 Sept. 2022.

Fazlollahi, M., et al. "Early-life Gut Microbiome and Egg Allergy." *Allergy*, vol. 73, no. 7, 15 Mar. 2018, pp. 1515-24, https://doi.org/10.1111/all.13389.

"Food-Specific and Component IgE Threshold Levels That Predict Food Allergy in People with Elevated Total Serum IgE Levels and Atopic Dermatitis." *Health, Biomedical and Clinical Sciences*, classic.clinicaltrials.gov/ct2/show/NCT03835767. Accessed 22 Aug. 2023.

Haahtela, Tari. "A Biodiversity Hypothesis." *Allergy*, vol. 74, no. 8, 4 Apr. 2019, pp. 1445-56, https://doi.org/10.1111/all.13763.

Han, Pei, et al. "The Association between Intestinal Bacteria and Allergic Diseases—Cause or Consequence?" *Frontiers in Cellular and Infection Microbiology*, vol. 11, 15 Apr. 2021, https://doi.org/10.3389/fcimb.2021.650893.

Hsiao, Kuang-Chih, et al. "Long-term Clinical and Immunological Effects of Probiotic and Peanut Oral Immunotherapy after Treatment Cessation: 4-year Follow-up of a Randomised, Double-blind, Placebo-controlled Trial." *The Lancet Child & Adolescent Health*, vol. 1, no. 2, Oct. 2017, pp. 97-105, https://doi.org/10.1016/s2352-4642(17)30041-x.

Lopez, Claudia M., et al. "Food Allergies." *StatPearls*, www.ncbi.nlm.nih.gov/books/NBK482187/. Accessed 24 July 2023.

Sestito, Simona, et al. "The Role of Prebiotics and Probiotics in Prevention of Allergic Diseases in Infants." *Frontiers in Pediatrics*, vol. 8, 22 Dec. 2020, https://doi.org/10.3389/fped.2020.583946.

Stefka, Andrew T., et al. "Commensal Bacteria Protect against Food Allergen Sensitization." *Proceedings of the National Academy of Sciences*, vol. 111, no. 36, 25 Aug. 2014, pp. 13145-50, https://doi.org/10.1073/pnas.1412008111.

Zhang, Shouling, et al. "Pathophysiology of Non-IgE-Mediated Food Allergy." *ImmunoTargets and Therapy*, vols. Volume 10, Dec. 2021, pp. 431-46, https://doi.org/10.2147/itt.s284821.