Priming the Paradox
Food Allergen Exposure & Intervention

Honors Thesis

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Introduction

According to the Center of Disease Control and Prevention (CDC), food allergies impact six percent of adults and eight percent of children in the United States.[1] Living with food allergies creates a multifaceted burden on the quality of life with strict dietary restrictions impacting psychological, social, and biological aspects.[2] Despite dietary restrictions and excessive measures for avoidance, accidental exposure to a food allergen can trigger an allergic reaction with symptoms ranging from mild oral irritation to life-threatening anaphylaxis.[2]

A variety of foods contain specific, allergenic proteins, with cross-reactive mechanisms to trigger IgE antibody release with allergen recognition. When considering why allergies would develop early on and potentially persist, it is important to understand how immunological, chemical, and environmental factors contribute to the human microbiome development and recognition to foreign substances like allergens. Despite allergens being most prevalent in children, adults are at a higher risk for adverse, life-threatening reactions such as anaphylaxis.

After years of dietary exclusion, food allergies to cow milk, hen eggs, soybeans, and wheat tend to diminish and resolve with age.[2] Meanwhile food allergies to peanuts, tree nuts, sesame, fish, and shellfish tend to persist and exacerbate with age.[2] There is currently no official cure for food allergies. However, allergists provide patients with an allergy management plan and individualized emergency medications, such as antihistamines or epinephrine injectors.[2]

Allergenicity versus Food Safety

Individual allergens differ from food safety and microbiological hazards in food. Allergens are considered a chemical hazard, meanwhile microbes from improper food safety are considered biological hazards. Food safety and microbiological hazards impact a broad consumer population and can be eliminated with heat processing. Meanwhile, individual allergens impact a specific population of people and may contain heat-stable proteins, which cannot be eliminated or diminished with heat. An example of a chemical hazard in fish that causes a Food Pseudo-Allergic (FPA) reaction is Scombroid Fish Poisoning (SFP). A FPA is a nonallergenic hypersensitivity due to immune cell activation from foods containing high levels of histamine. Due to improper storage of scombroid fish, Gram-negative, saprophytic bacteria on the flesh overgrow and produce histidine decarboxylase, an enzyme that breaks amino acids into histamine.[14] Inflammatory symptoms from SFP resemble those in allergies despite not being IgE-mediated, because the symptoms are caused by histamine. In SFP, IgE antibodies are not impacted, and external histamine mediates a reaction.[14] Meanwhile, food allergic reactions are triggered by IgE antibodies and rapid release of histamine from immune cells.

Immunology

Immunoglobin E

IgE antibodies are located on immune cell surfaces such as mast cells, basophils, and eosinophils.[3] These cells are located at the respiratory tract, gastrointestinal tract, and urinary tract; however, trace amounts of IgE antibodies can be detected in blood.[3] IgE antibody production increases when it recognizes a non-self antigen, such as a food allergen. IgE antibodies are mucosal antibodies, which fight off non-self antigens from pathogenic parasites and non-pathogenic food allergens.[3] In food allergies, allergens are recognized as harmful pathogens to mediate Ig E symptoms that can range from mild hives to severe, life-threatening anaphylaxis. However, it is common for IgE to recognize nonpathogenic proteins, like food allergens as harmful pathogens.[3]

Normal total IgE levels are determined by individual physiological characteristics and range between 1.5 to 150 kilounits per liter (kU/L).[3] If IgE levels for a specific antigen are above 0.35 kU/L, this indicates allergenicity to a specific substance.[3] Some common conditions with exacerbated IgE levels include asthma, food allergies, hives, rheumatoid arthritis, and hyper IgE syndrome.[3] Besides the previously mentioned symptoms, high IgE levels can also cause eczema, yeast infections, pneumonia, and lung abscesses.[17]

Immunoglobin G

IgG (immunoglobin G)-mediated reactions are associated with delayed, non-allergenic immunological reactions, like food intolerances.[4] Unlike IgE antibodies, IgG is not located on immune cell walls where histamine is produced. IgG is found in bodily serums, like blood and lymph fluids.[4] Increased IgG can enhance intestinal permeability, so foreign proteins, like food allergens, can easily enter the bloodstream to trigger additional IgG production.[4] This mechanism causes a delayed cascade of reactions, from initial food ingestion to IgG antibody production, triggering systemic, delayed symptoms.[4]

IgG antibodies travel in bodily serum to reach a destination, like the gastrointestinal tract or placenta, to mediate an immunological reaction, which explains why IgG-mediated reactions are gradual and delayed. Meanwhile, IgE-mediated reactions have an immediate onset, because immune cells already contain IgE and continue to produce larger amounts when an allergen is present.[4] The delay in symptom onset from IgG-mediated food reactions results in many being chronically underdiagnosed.[4] Some IgG-mediated symptoms associated with underdiagnosis are gastrointestinal symptoms, such as cramps, diarrhea, and constipation.[4]

Notably, an IgG-mediated food intolerance can trigger systemic conditions such as irritable bowel syndrome (IBS), hair loss, chronic fatigue, and migraines.[4] IBS is associated with neurological and chronic gastrointestinal symptoms.[4] IBS is associated with symptoms which resemble an IgG-mediated food intolerance, which also increase IgG production and reduce production of anti-inflammatory cytokines.[4] Historically, food elimination has been recommended for those with IgG-mediated IBS, enzymatic deficiencies, or IgE-mediated food allergies, which can contribute to the development of nutritional deficiencies.[4,5]

IgE versus IgG-mediated Reactions

Food allergies are adverse reactions to heat-stable, food allergens, which cause immune cells to further increase the production of IgE (immunoglobin E) antibodies.[1] Immediate food allergies are most common and associated with IgE antibodies; meanwhile, delayed food reactions are associated with IgG antibodies.[6]

Similar symptoms between IgG and IgE-mediated immune reactions include hives, nasal inflammation, rashes, and asthma.[4] A study from Annals of Saudi Medicine analyzed patients who tested negative for IgE-mediated allergies but suffer from allergy symptoms like skin hives and asthma. [4] A large majority of patients, who tested negative for IgE antibodies, ended up testing positive for food specific IgG antibodies with common triggers linked to wheat, egg white, pistachios, and cow milk.[4]

Confusion between the mechanisms of IgE and IgG antibodies can result in late diagnosis and financial burden due to improper testing.[4] However, a novel IgG-specific food sensitivity test called IBS ELISA (enzyme-linked immunosorbent assay) was designed to assess IgG-specific reactions to 18 common foods.[7] IBS ELISA is less likely to have false-positive results compared to an IgE skin-prick test. Unlike a skin-prick test, ELISA tests general antibodies rather than IgE-specific antibodies from a targeted allergen. The information provided from an ELISA assay can inform a patient about their antibody production and protein content to create an individualized diet to aid reducing delayed, IgG-mediated food sensitivities.[7]Although the ELISA test takes longer and is more expensive than a skin-prick test, it has a higher specificity for diagnosing IgG-mediated syndromes and does not interfere with skin conditions, allergies, or medications.[7]

Skin-prick tests can only determine the presence of food-specific IgE antibodies and cannot be used to diagnose IgG-mediated food syndromes. [4,7,25] IgE antibody production increases on immune cell surfaces as a response to a foreign antigen, like food allergens. However, IgG antibodies are carried throughout bodily serums prior to arriving at their destination to elicit milder, delayed symptoms. Therefore, the IgG-specific IBS ELISA test has the potential to diagnose those with IgG-mediated gastrointestinal symptoms.[7] Meanwhile, a skin-prick test is completed by an allergist, who administers a patient with food allergen prick and control. If a skin reaction, such as hives or a wheal, emerge with a skin-prick test, the results for an IgE-mediated allergy are positive.[25]

Conformational & Linear Epitopes

Epitopes are recognizable regions on the antigens of allergens, they are located on an allergen surface and are easily accessible for IgE antibody binding.[8] Epitopes can be conformational or linear, but food processing can alter conformational epitopes via unfolding or aggregation.[8,9] A linear epitope is mostly resistant to food processing and maintains its ability to bind IgE antibodies because of its continuous, primary amino acid sequence. [8] Meanwhile, a conformational epitope is a discontinuous and folded complex. Conformational epitopes consist of amino acids that are spatially close but sequentially distanced within a folded 3-D protein.[8]

Conformational epitopes become exposed or masked with simple food processing mechanisms, which unfold and aggregate food allergens by heat treatment.[9] These denatured conformational epitopes mask into neo allergens, so IgE antibodies are unable to bind and elicit allergic reactions.[8] Neo allergens are new, altered allergenic structures produced during food processing. Food processing techniques can alter allergens by reducing, eliminating, or

modifying allergen fold structure to destroy or create new epitope binding sites for IgE antibodies.[10]

Meanwhile, linear epitopes are relatively heat-resistant but impacted by enzymatic hydrolysis and the Maillard reaction.[8] Protease enzymes added or found in food can cleave peptide bonds in allergens, which can disrupt linear epitope structure by enzymatic hydrolysis.[8] In addition to unfolding and aggregation in conformational epitopes, heating can induce the Maillard reaction, which occurs in the presence of reducing sugars.[8] Typically heat stable allergens have linear epitopes, which cannot undergo heat-induced folding; therefore, they are prone to epitope masking and persistent allergies.[8] Epitope masking occurs when heat treatments and additional physiochemical conditions, such as glycation or aggregation, alter food allergen epitopes to become unrecognizable by IgE antibodies and unable to elicit an allergic reaction.[8] An allergen with a linear epitope maintains structural integrity during food processing and digestion, which is why it can cross the epithelial barrier and elicit an immunological reaction.[8]

Epitope Recognition

Cytokines assist with regulating inflammation, antibody production, and the onset of allergy symptoms. Cytokine specific signaling pathways dictate T-cell subset, because it impacts which epitopes a T-cell can recognize.[11] T-cells can either be differentiated under subsets, Th1 and Th2.[11] Th1 refers to Type 1 T-helper cells, which mediate intracellular infections and organ-specific autoimmune diseases.[11] Th1 are associated with IgG antibodies and building a tolerance to intracellular infections.[11]

Meanwhile, Th2 refers to Type 2 T-helper cells, which activate immune cells to recognize extracellular parasites, like helminths.[11] Th2 cytokines include interleukins (IL) such as IL-4, IL-5, and IL-13.[11] Th2 promotes IgE production via IL-4 when presented with a food allergen epitope.[11] Th2 are associated with IgE antibodies, because they activate atopic manifestations and allergic reactions.[11] Allergen-Associated Molecular Patterns (AAMP) are repetitive, recognizable structures located on food allergens bind to innate immune receptors to activate cytokine signaling and elicit Th2, IgE-mediated symptoms.[11,12] AAMPs impact the initiation of an allergy, because identical epitopes in proximity bind to IgE at once to mediate an intense allergic reaction.[11] In response to food allergen epitope recognition by IgE antibodies, Th2 cells produce cytokines to activate B-cells and combat extracellular antigens with IgE production and mast cell activation.[11]

Primary Exposure

Infant Microbiome

A biological hazard like a food safety outbreak can impact diverse populations; meanwhile, allergens target specific individuals via immunological or non-immunological reactions.[15] Food allergies are triggered by allergenic proteins and can elicit dangerous symptoms. Meanwhile, food intolerances are mild, non-immunological reactions caused by enzymatic deficiencies. To develop an immunotolerant gut, early microbial colonization in the intestines is vital during an infant's first six months of life.[16] Food sensitizations are enhanced by a microbial imbalance in the gut, which can appear as reduced microbial diversity or an abundance of undesirable microbes such as the *Enterobacteriaceae* and *Bacteroidaceae*.[16] Increased levels of these specific bacteria can result in reduced amounts of beneficial strains like *Bifidobacteria* and *Clostridia*.[16] The mother's gut microbiome influences infant microbiome from birth, which is why early intervention to prime protective immunity is essential. For example, infants born by C-section are more prone to developing allergies due to lack of exposure and colonization by maternal vaginal microbiota.[16] In addition, not breastfeeding or regulating infant fiber intake can inhibit the growth of beneficial, probiotic bacteria.[16]

Hygiene Hypothesis

In 1989, British epidemiologist, David Strachan, observed that larger families are less likely to develop hay fever.[18] These findings led him to hypothesize that allergy onset can be prevented with early childhood infections that prime their immune systems.[18] The hygiene hypothesis states that the reduced incidence of infections in developed Western nations is the main contributor to the increasing prevalence of autoimmune diseases and food allergies.[17]

Developed countries are associated with better public health measures, such as improved sanitation and medical access to vaccinations and antibiotics.[17] For example, infant birth via C-section is becoming a popular alternative to a traditional childbirth. A C-section deprives an infant from prenatal exposure to maternal and sibling microbes. This cleanliness deprives the immune system from exposure to beneficial, immuno-protective microbes and exponentially reduces immunoregulation.[18]

Strachan suggested that increasing rates of allergies are correlated with a “post-industrial epidemic”, which can be a result of reduced opportunities for cross-infections amongst younger families, who adhere to contemporary hygiene.[18] Contemporary hygiene methods, such as excessive cleanliness around infants have reduced overall rates of microbial exposure to humans.[18] These measures do not prime an infant’s immune system for future interactions with older humans with diverse microbiomes. Limiting microbial exposure to infants will enhance the risk of atopic manifestations and limit the ability of protective immunity.

In the 1990s, allergies and hay fever incidents were reduced amongst anthroposophic, farming families, and specifically families with more siblings.[18] These individuals are believed to have been earlier exposed to hygiene-related allergy determinants, such as external microbial

infections from agri-environmental surroundings or older siblings. [18] Furthermore, the prevalence of self-reported hay fever from participants 11 to 23 years old was most common in upper class citizens and becomes less prevalent with age.[18]

Rates of appendicitis have risen since water cleanliness standards have become stricter causing reduced exposure to enteric microbes, such as *Bacteroidetes*.[18] Furthermore, a study conducted in Russia and Finland revealed that Finland's microbe-free drinking water is enhancing pollen sensitizations and onset of atopy in Finnish children.[18] Meanwhile, Russia's drinking water has a high microbial load, and children are not sensitive to pollen and do not have atopic reactions.[18] Overall, improvements in hygiene are reducing rates of infection in childhood, which, while reducing infant mortality has been depriving children of protective immunity and furthering their risk of developing atopy.[18]

On the other hand, developing countries are associated with increased rates of infectious diseases due to poor microbial quality of consumables like food and water.[17] In 1976, a study was conducted to compare the prevalence of allergies and infectious diseases between an impoverished Native American village and its neighboring white community.[18] The Native American population had higher IgE levels and were less susceptible to eczema, bronchitis, hay fever, and hives, compared to its neighbors.[18] However, the Native American population was susceptible to parasitic helminths, which are believed to provide infected individuals with a protective effect on immunity after a primary infection.[18] IgE antibodies released from immune cells are responsible for parasitic defense against helminths.[18]

Based on the study, a contemporary reduction in parasitic exposure has led the immune system to misdirect towards a Th2 response towards nonpathogenic antigens found in food and

environmental allergens. With reduced exposure to parasites and bacteria, the immune system remains unprimed and intolerant, so increased levels of IgE will elicit more intense symptoms.[11,18] Exposure to small, beneficial amounts of microbes from a variety of sources such as farm soil, livestock, drinking water, and unpasteurized foods in developing countries diversify the human gut microbiota in ways the lifestyle of a developed nation could not achieve.[17,18]

Allergen-Associated and Related Syndromes

Oral Allergy Syndrome (OAS)

Oral Allergy Syndrome (OAS), also known as Pollen Food Allergy Syndrome (PFAS), is a mild, IgE-mediated allergic reaction due to the cross-reactivity between similar antigens found in pollen and food.[19] OAS is also known as PFAS, because seasonal allergies dictate how individuals react to different food allergens.[19] For example, if one has an allergy to birch tree pollen during the spring, then allergic reactions may be triggered by carrots, nuts, or pitted fruits due to similar allergen structures causing cross-reactivity.[19] Meanwhile, those with allergies to grass may trigger reactions from melons, oranges, peaches, and tomatoes.[19]

In food allergies, cross-reactivity occurs when an allergen associated with a specific food elicits allergic reactions due to the structurally similar allergens.[10] Structurally similar allergens cross-react to mediate IgE symptoms in individuals with OAS. For example, soybean allergens, like Gly m 3 and Gly m 4 have structurally similar allergens to Bet v 1 or Bet v 2 in birch tree pollen.[10] An OAS diagnosis utilizes the same tests as other IgE-mediated reactions and environmental allergy shots to mediate cross-reactivity is a common recommendation.

OAS symptoms emerge immediately after consuming raw produce or nuts, which include irritation to the oral cavity.[19] It is rare for OAS to cause severe reactions; however, it is possible. Anaphylaxis reduces blood pressure and narrows blood vessels, resulting in immediate onset of severe symptoms impacting respiratory, gastrointestinal, and skin-related organs.[2,19] Anaphylaxis causes severe throat swelling, resulting in difficulty breathing or swallowing.[2,19] Anaphylaxis is a

rare OAS symptom, however it can occur in highly allergic individuals with cross-reactivity to environmental allergens like pollen. [19]

Occupational Asthma & Cross-Reactivity

Occupational asthma can occur in agriculture and factory workplaces, where individuals are frequently exposed to aerosolized, processed allergens such as eggs, wheat, nuts, and seeds.[20] For example, bakers, who have been exposed to high levels of wheat flour and aerosolized eggs, are at risk for developing occupational allergies.[20,21]

Individuals who work in pet food manufacturing or insect laboratories are more likely to inhale insect particles, which can be prevented by using proper protective equipment. [22] These workers are at a higher risk for developing allergies or becoming sensitized to insect aeroallergen, tropomyosin. Troponin C (TnC) proteins, which bind calcium, are cross-reactive between cockroaches, dust mites, and shrimp.[22] This phenomenon explains why individuals with shellfish allergies are prone to severe asthma symptoms when exposed to household insects, like mites and cockroaches.[22]

Sulfite Allergenicity

An example of an ingredient that triggers allergy-like symptoms is sulfites, which are additives used to prevent oxidation and to buffer pH.[23] Their ingestion, like IgE-mediated OAS, is linked to aeroallergens and worsening asthmatic symptoms.[23] For example, sulfites are used as a preservative in wines, and sulfites release sulfur dioxide gas to trigger allergy-like symptoms in sensitized individuals. An urban study was done in Poland and Sweden and determined that an

increased exposure to pollutants, like sulfur dioxide or smoke particles, reduces allergic sensitizations.[18]

For those with allergies to sulfite-containing foods, it is recommended to avoid acidic and fermented foods, which are known to contain greater than 50 ppm sulfite.[24] In addition, sulfites are commonly found in pharmaceuticals, cosmetics, and cleaning products.[23] Unlike IgE-mediated symptoms, exposure to respiratory irritants like sulfur dioxide from sulfites will worsen sensitization, despite frequent exposures providing temporary acclimatization.[18,23,24] Those frequently exposed to sulfur tend to increase IgE production, which causes sensitization and promotes chronic inflammation.[18,23,24]

Food Protein Induced Enterocolitis Syndrome

Food Protein Induced Enterocolitis Syndrome (FPIES) can begin during the first year of an infant's life and a diagnosis is common after 1 to 3 years.[13] FPIES is a non-IgE-mediated gastrointestinal food allergic disorder, but its symptoms are more severe than the acute intolerance-like symptoms seen in IgG-mediated allergies.[13] FPIES commonly emerge in infants when they are being introduced to a new food.[25] Like IgG-mediated allergies, this gastrointestinal (GI) reaction occurs 2 to 6 hours after consuming milk, soy, and solid allergens like grains.[13] FPIES is an intense systemic allergy, so symptoms vary from vomiting to shock.[13]

A milk allergy misdiagnosis is common when attempting to diagnose FPIES, because these syndromes can be triggered with dairy resulting in gastrointestinal symptoms.[25] Additionally, the gastrointestinal symptoms in infants mimic bacterial or viral infections, so diagnosis is commonly delayed.[25] Dehydration is the most common symptom of FPIES, so rehydration via IV is recommended.[25] Since FPIES is non-IgE mediated, skin-prick and blood

allergy diagnosis tests cannot be used for diagnosis.[25] An oral food challenge (OFC) would be applicable for a FPIES diagnosis because symptoms are chronologically monitored to see if a delayed allergic reaction or gastrointestinal symptoms appear.[25]

Diagnosis, Intervention, & Treatment

Oral Food Challenge (OFC)

Individuals with allergies are not allergic to all parts of a specific food, but rather to allergenic proteins found within a food, which is why it can be difficult to officially diagnose food allergies with skin-prick tests and blood tests. [25,26] Skin-prick tests have high false-positive rates and have difficulty distinguishing sensitization from allergies. [25,26] Individuals with either sensitization or allergies have antibodies for corresponding allergens. However, sensitization differs from allergies, which produce additional IgE-mediated allergy symptoms. In addition, foods contain many proteins and only some of them are allergens, which are resistant to heat, digestion, and food processing.[27,28] Food allergens and environmental allergens can cross-react due to structural similarities, which is why both can elicit similar allergy symptoms. Furthermore, botanically similar foods, like peanuts and soybeans, can cross-react.[27,28] Because of the difficulties associated with these diagnostic tests, oral food challenges (OFC) are often used.

During an OFC, an allergist will administer low allergen doses of food to a patient, and the doses increase if no reactive symptoms emerge.[26] An OFC will stop once the patient has any sort of physical symptoms, even those as mild as flushing.[26] If an individual demonstrates no symptoms after consuming a suspected allergen, they will not meet the criteria to be diagnosed with an allergy.[26] Typically, fewer than half of allergic individuals undergo a reaction during an OFC.[27] An OFC used in combination with a skin-prick test or blood test can provide a more accurate food allergy diagnosis, but also has the potential risk of triggering a reaction with increasing allergen doses.[26]

When an OFC is performed, allergen-containing foods that have undergone heat treatments and food processing are used because of their reduced allergenicity. For example, an OFC for cow milk allergy would use dried milk powder, whose epitope structure has been changed with heat treatment.[13] Therefore, if patients become tolerant to baked milk, but continue to react to untreated milk, it is likely that a tolerance can develop to milk-containing products.[13]

Like milk, heat stability of the antigens is an important consideration when administering an OFC for eggs, because raw eggs, scrambled eggs, and eggs present in pastries will cause variations of allergenicity based on their degree of physiochemical alteration.[8] Some individuals are only allergic to raw eggs and not heat treated eggs, because egg white protein structure and solubility changes with heat.[8] Different forms of egg-containing foods demonstrate different levels of immunoreactivity because of differences in protein and allergen structure. Structural changes can reduce egg allergenicity, because allergen epitopes become masked, modified, or destroyed. Therefore, food allergens cannot bind to IgE antibodies to signal the release of histamine.[8]

Oral Immunotherapy (OIT)

OIT is used for increasing tolerance for IgE-mediated allergic immune responses, and not food intolerances from enzyme deficiencies. Oral immunotherapy (OIT) exposes patients to small amounts of a specific allergen with the intentions of desensitization and building a tolerance, instead of encouraging strict avoidance.[28]

Infants receive their primary nutrients from maternal breastmilk until their transition to solid foods at 6 months old.[29] The first step of OIT is to introduce low allergy risk foods, wait a couple of days before introducing a new food. After each subsequent food the infant will be

observed to see if there are an allergic reaction or gastrointestinal symptoms.[29] Once a food is determined to contain an allergen, then foods will be introduced at increasing doses.[29]

Food oral immunotherapy (OIT) increases micro-dosages of a suspected allergen, and it is administered biweekly to reduce allergen sensitization by building tolerance.[30] OIT can be designed to target a single allergen or multi allergens.[2] OIT exposes patients to trace amounts of an allergen with a goal of causing no symptoms, but mild-to-moderate allergic symptoms can occur and are treatable with an epinephrine shot.[2] OIT's primary stage consists of slowly increasing the allergen dose for a few months.[2] During the primary phase, it is most common for the onset of allergy symptoms, such as rhinitis, gastrointestinal stress, and atopic dermatitis.[2] Once a maintenance dose is reached, the final phase begins and consists of regular ingestion of a dosed allergen.[2] OIT can be administered via food or oral supplements. This treatment is long-term because it does not cure an allergy and allergen sensitization resumes when treatment stops.[30]

It is important to diagnose food allergies at a young age, because a child's immune system is more responsive to treatment interventions.[2] OIT is a popular choice for actively managing a food allergy, because it also provides desensitization protection from trace allergen exposures such as allergens from cross contamination.[2]

OIT poses acute risks such as skin rash, oral itching, and stomach cramping.[30] Due to OIT causing oral reactions, eosinophilic esophagitis (EoE) can develop during OIT and cause chronic esophageal inflammation, difficulty swallowing, and gastrointestinal symptoms.[30] Around three percent of OIT patients with food allergies experienced EoE as a complication of treatment but it resolved with discontinuation of OIT.[16] Another downside to OIT is how its

threshold and allergen reactivity is easily reduced by external factors, such as viral diseases, female menstruation, and physical activity.[16]

OIT continues to be the standard line of treatment because desensitization is effective in building long-term tolerance to food allergens. Epinephrine injections are used for treatment of an acute allergic reaction.[30] The injections contain adrenaline and immediately increase blood flow to assist with life-threatening respiratory symptoms.[30] The injections significantly differ from OIT, subcutaneous immunotherapy and anti-IgE injections because of the use in acute responses.[30] Because of the possible exposures and other limitations (as mentioned above), it is vital for OIT patients to continue to carry emergency epinephrine injectors in case of anaphylactic shock from an allergic reaction.[30]

Subcutaneous Immunotherapy (SCIT)

Like OIT, subcutaneous immunotherapy (SCIT) injections are a long-term treatment to provide long-term relief for environmental, inhalant allergens found in pollen, dust, mites, pet dander, and mold.[31] SCIT is specifically used for IgE-mediated environmental allergens and aeroallergens.[31] SCIT cannot be used for IgE-mediated food allergies due to the risk of cross-reactivity with environmental allergens.[31] SCIT injections administer gradually increasing doses of a suspected allergen to prime the immune system to become desensitized to environmental allergens.[31] When SCIT begins, patients are injected weekly to establish a dose to treat patients once a month for three to five years.[31]

SCIT injections are used to treat year-round, environmental allergies and are commonly prescribed with steroid and asthma medication.[31] Systemic reactions are common with SCIT but are easily manageable in a clinical setting.[31] Like OIT, SCIT does not cure environmental allergies, but instead provides long-term relief by desensitizing individuals and reducing allergy symptoms.[31]

Anti IgE Injection

In 2024, the FDA approved Omalizumab, a monoclonal anti-IgE injection treatment, used every 2 to 4 weeks, that blocks IgE antibodies in the blood and reduces IgE receptors on the immune cells.[31,32] Since the injection binds to the antigen receptors, it prevents allergen stimulation, histamine release, and inflammatory-associated symptoms.[32] The monoclonal antibody injection is dosed based on patient body weight and amount of IgE present in a blood sample before treatment.[31] Omalizumab aids building multi-allergen tolerance by providing temporary relief to IgE-mediated food allergy symptoms within 24 hours.[31] Despite Omalizumab's relief, it does not function similarly to epinephrine.[31,32] Epinephrine is an immediate acting injection used to treat anaphylaxis, while Omalizumab is a monoclonal antibody that aids allergy prevention.[31,32]

From a 2025 clinical study, Omalizumab was found to be the best holistic treatment for treating multiple food allergies, compared to OIT which administers increasing concentrations of a singular food allergen to build tolerance.[32] This novel, immediate-acting injection is revolutionary in multi-allergen treatment, because many patients quit OIT due to chronic, adverse symptoms from minimally increasing allergen exposure.[32] In addition, anti-IgE injections are safer, provide immediate bioavailable relief, and are most effective for treating multi-food allergies. [3]

The "Big Nine" Food Allergens

Introduction

The "Big Nine" allergens include cow milk, hen eggs, wheat, soybeans, peanuts, tree nuts, sesame, shellfish, and fish.[1] The allergens known to diminish and/or disappear with age include cow milk, hen egg, soybeans, and wheat.[2] On the other hand, allergens that are known to persist with age include peanuts, tree nuts, sesame, fish, and shellfish.[2]

Cow Milk Allergy (CMA)

Cow milk allergies impact two to three percent of the general population.[12] CMA is most prevalent during childhood and is known to resolve before adolescence.[12] Infants drink their mother's breast milk for the first three months of life. Then around four to six months old, they are exposed to non self-antigens from cow milk to induce an allergen tolerance.[13] Since less infants are breastfed, contemporary lifestyle is hypothesized to impact CMA prevalence because more infants are supplemented with dried milk, infant formula.[12,13] Breast milk is the best option to prime an infant's immune system because it stimulates the production of immunomodulatory proteins and cytokines, which ease cow milk consumption.[12]

Milk pasteurization is a heat treatment which uses specific temperatures to target the elimination of food pathogens without impacting the nutritional value. Pasteurization removes food pathogens and does not alter milk allergenicity.[13] During milk pasteurization, it is vital to consider thermal conditions, treatment times, and surrounding nutrients to optimize milk protein structure.[13] For example, when milk is heat-treated in the presence of wheat, there is reduced binding between specific IgE and casein proteins.[13] This phenomenon explains why some

individuals with CMA can consume items like pastries or crackers, because milk is processed and not the primary ingredient.[13] With the application of heat and enzymes during industrial processing via acidification, pasteurization, and sterilization, the primary, secondary, and tertiary allergen structures of milk can be altered.[12]

The main allergenic molecules in milk include caseins, and whey proteins like lysozymes such as alpha-lactalbumin (Bos d 4) and lipocalins like beta-lactoglobulin (Bos d 5).[12,28] Whey proteins are heat-labile compared to casein proteins, so they are most prone new epitope formation with milk processing.[12] In whey, Bos d 4 regulates mammalian lactose production, bone formation, and has two calcium binding sites.[13] Bovine Bos d 4 immunologically differs from human Bos d 4, which explains why infants exposed to breast milk can experience sensitization from Bos d 4 allergens when ingesting cow's milk.[13]

Bos d 5 and alpha caseins are not found in breast milk, unless the mother has been drinking mammalian milk, which contains those proteins.[12] Bos d 5 is a lipid-binding whey protein with multiple exposed epitope sites that can be recognized by IgE antibodies in allergic individuals.[13] Allergies to Bos d 5 are associated with persistent CMA because it has multiple epitope binding sites for IgE to attach to after milk ingestion.[13] Heat-labile, whey proteins contain conformational epitopes and are prone to processing changes; therefore, high levels of IgE antibodies against Bos d 4 and Bos d 5 are associated with persistent CMA, because IgE production correlates with epitope recognition.[13] Symptoms that correlate with persistent CMA include multiple foodborne allergies, heightened IgE levels, asthma, allergic rhinitis, acute skin reactions and immediate symptoms upon milk consumption.[33]

Casein molecules have hydrophobic centers and hydrophilic peripherals to form hetero multimer micelles consisting of four distinct allergenic proteins Bos d 9, Bos d 10, Bos d 11, and Bos d 12 .[12] Unlike whey proteins, casein proteins are heat-resistant because they contain more complex, quaternary structures with linear epitopes.[13] Casein's micellular configurations are susceptible to digestive acids and proteinases, despite being heat-resistant.[12,13] Interestingly, casein proteins like alpha-s1-casein (Bos d 9) and beta-casein (Bos d 11) are associated with calcium-binding and major IgE sensitization.[13]

For those with CMA, milk and dairy product avoidance is recommended, because highly homologous allergens are found in different types of herbivorous, mammal milk.[13] Cow milk and buffalo milk contain Bos d 9 casein and Bos d 5 whey proteins, so cross-reactivity is common.[13] The amount of protein presented can impact allergy severity. For example, proteases from microbial fermentation disrupt IgE's ability to bind epitopes, because the complex allergen is broken down to simple peptides and amino acids.[13] Homogenization enhances lipid droplet surface area by the breakdown of fat globules to facilitate protein attachment to lipids. Unlike fermentation, homogenization can enhance allergenicity to Bos d 5, because lipid droplets expose an allergen surface which triggers an Ig-E mediated reaction.[13] It is difficult to target cow milk allergens using heat-treatment, because casein proteins have complex, heat-resistant structures; meanwhile, whey proteins are heat-labile and pose a neo allergenic risk.[12,13]

Hen Egg Allergy (HEA)

Hen egg allergies account for thirty-five percent of food allergies in children. [6] Typically, HEA emerges during the first year of life with a typical diagnosis at 10 months old.[34] When infants are being introduced to solid foods, primary exposure to eggs can trigger an allergic

reaction in sensitized individuals. Sensitization to hen egg is hypothesized to emerge in utero, from breast milk, or from dermal exposure prior to gut mucosa exposure.[34] The development of a tolerance to egg allergens is indicated by a rapid decline of allergen-specific IgE with age, which supports the common occurrence of an early HEA diagnosis, less severe symptoms, and allergy resolution with age.[34]

The egg white contains the four major immunodominant allergens, which is why it is known to be more allergenic than the yolk.[6] The four allergens in egg whites are ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovotransferrin (Gal d 3), and lysozyme (Gal d 4).[6] Egg whites can be heated to unfold, denature, aggregate, and coagulate allergen structure.[8] These changes to allergen structure impact its epitopes and ability to bind to IgE, which is why allergenicity is reduced.[8] Gal d 2 is the most abundant protein in eggs, however its heat lability changes conformational epitope structure to reduce allergenicity.[8]

Gal d 1 is a highly glycosylated protein with strong disulfide bonds, which is why it is associated with heat stability, moderate digestibility, and high allergenicity. It has linear epitopes, which are heat-resistant and maintain structural integrity upon processing.[8,29] Like cow milk allergens, Gal d 1 allergenicity reduces in the presence of gluten and excessive heat, because denatured Gal d 1 aggregates with gluten proteins.[8] When egg is heated with gluten, aggregation reduces the availability of conformational epitope for IgE recognition and binding.[8]

Despite its lability to heat and digestion, alpha-livetin, known as Gal d 5 is the main allergen in egg yolk and is associated with bird egg syndrome.[8,29] Bird egg syndrome is an example of allergen cross-reactivity. Individuals sensitive to aeroallergens from bird feces can have secondary sensitizations to Gal d 5 which causes respiratory symptoms.[34] Gal d 5 in hen

eggs and poultry meat is cross-reactive with quail and duck eggs, so it is important for individuals with HEA to be cautious.[1,34] Due to hen egg allergen cross-reactivity, it is used as an indicator for asthma and aeroallergen sensitivity.[35]

Five to seven percent of children are impacted by egg allergies; meanwhile, only two to three percent of adults have it because of resolution around ages 5 to 7 years old. [6] Research demonstrates that egg-allergic individuals with IgE antibodies reactive to linear epitopes tend to have persistent allergies, while those with IgE antibodies reactive to conformational epitopes tend to have allergies that diminish with age.[34]

Despite being the second most prevalent allergy, persistent HEA is heavily associated with early-onset, moderate-to-severe atopic dermatitis (AD) and EoE in sensitized individuals.[34] Those with persistent HEA have high specific IgE levels to Gal d 1, which is heat stable but moderately digestible. Digestion can reduce Gal d 1 allergenicity, which explains why skin reactions are more common in persistent HEA, because uncooked eggs contain Gal d 1 allergens, which have linear epitopes.[34]

Wheat Allergy

Following CMA and HEA, wheat allergies are the third most common food allergy. Wheat allergies impact one percent of children and twenty hundredths of a percent of the global population.[36,37] However, two-thirds of children outgrow their allergy by age twelve.[36,37] Like CMA and HEA, a wheat allergy triggers IgE-mediated symptoms that can range from mild respiratory and gastrointestinal symptoms to severe, life-threatening anaphylaxis.[37] In addition, a wheat allergy diagnosis consists of skin-prick tests and IgE blood serum tests, similar to a diagnosis for CMA or HEA.[37]

Those with wheat allergies are recommended to avoid consuming gluten-containing products and to carry an epinephrine injector as a precautionary measure.[37] Within minutes to hours of exposure to wheat, symptoms onset and blood pressure drops, which increases risk of anaphylaxis. It is difficult to recommend avoidance as an effective treatment method because the global incidence of food allergies, rapid development of food industries, and allergen cross-contamination are becoming more common in contemporary times.[21]

Oral immunotherapy (OIT) can assist in desensitizing and modifying immunological responses to wheat.[21] Unlike CMA and HEA, there are safety concerns with wheat allergy OIT due to the onset of severe symptoms, like anaphylaxis, during the dose escalation phase.[21] The development of non-allergenic and hypo-allergenic wheat products revolutionized OIT for wheat allergies.[21] Wheat OIT patients are dosed primarily with non-allergenic wheat, hypo-allergenic wheat, and then finally wheat to ensure proper dose escalation.[21] Food processing methods like fermentation, deamidation, enzymatic treatments, and heat treatments reduce wheat allergenicity by changing gluten epitope structure.[21]

Celiac disease, gluten intolerance, and wheat allergies are adverse gluten-related reactions with different underlying, immunological mechanisms.[36,37] Mild gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhea are common symptoms.[36] A wheat allergy differs from Celiac disease and gluten intolerance because severe, IgE-mediated symptoms can arise, such as anaphylaxis, respiratory sensitization, and atopic dermatitis.[21,36]

Celiac disease is an autoimmune disease with a similar prevalence to wheat allergies.[37] For those with Celiac disease, gluten consumption causes IgA antibody production, which damages the lining of the small intestine to elicit gastrointestinal inflammation.[36,37] IgA

antibodies are responsible for protecting gut mucosa barrier entrance points from food allergens and pathogens.[36,37] Gluten intolerance is also known as non-Celiac gluten sensitivity; it is demonstrated with a negative Celiac disease test but with gastrointestinal sensitivity resembling Celiac disease upon gluten consumption.[36]

Wheat is the most common grain grown and consumed in the United States.[37] Individuals with wheat allergies are advised to consume corn, oats, quinoa, rice, and other non-gluten grains to meet nutritional needs.[37] However, twenty percent of wheat allergic individuals are allergic to multiple grains, which is why cross-reactivity is a vital consideration for allergy management.[21] Wheat allergen cross-reactivity typically occurs after consuming grains, like barley and rye.[21] Wheat flours are traditionally used for baking; however, gluten-free blends are being formulated to produce a product that resembles wheat flour.[37] Wheat is found in pastries, bread, pasta, flour, and breakfast cereals.[37] For individuals allergic to wheat, caution is advised when consuming gluten-containing products such as plant-based meat alternatives, soy sauce, glucose syrup, and surimi.[37] It is vital to read food ingredient labels, because gluten can be a hidden allergen in items such as beer, fried foods, sauces, processed meats, and modeling clay.[37]

The scientific nomenclature for wheat is *Triticum aestivum L.*.[21] Wheat allergens are found throughout its structure and include Tri a 14, Tri a 19, Tri a 20, and Tri a 36.[21] Wheat proteins are classified into three categories: gliadin, glutenin, and soluble proteins.[21] Gliadin proteins impact individuals with either wheat allergy or Celiac disease.[21] A-gliadin is associated with small intestine inflammation and permebility.[21] Meanwhile, y-gliadin is associated with IgE-mediated, wheat-dependent, exercise-induced anaphylaxis (WDEIA) in those with wheat allergies.[21] Glutenin proteins are associated with Celiac disease and contact dermatitis.[21]

Nutrient-rich, soluble proteins include albumin and globulin, and consist of major allergens involved in baker's asthma, wheat allergies, and WDEIA.[21]

Physical, chemical, and biological methods can alter wheat allergenicity by inactivation or denaturing epitope structure.[21] Physical methods include high hydrostatic pressure (HHP), heat, irradiation, and ultrasound.[21] These methods are cheap and efficient; however, they contribute to nutrient-loss and can enhance allergenicity by forming novel, antigenic epitopes.[21] Wheat allergenicity is reduced with long heat treatments and the occurrence of the Maillard reaction.[21] HHP is considered highly effective at maintaining the food safety and nutritional aspects in wheat; however, this physical method can result in neo allergen formation.[21] Chemical methods include glycosylation, deamidation, and treatments using enzymes and acids.[21] These methods maintain functional and nutritional properties, while altering epitope structure.[21] Some risks with chemical methods include changing product physiochemistry, generation of neo allergens, and byproducts impact consumer perspective on quality.[21] Biological methods consist of fermentation and genetic engineering, which are the most effective methods in reducing wheat allergenicity with their use of proteases, similar to cow milk.[21] These methods are precise, efficient, and maintain nutrients; however, they are novel and complex.[21]

Soy Allergy

Like CMA and HEA, soy allergies emerge in children under three years old and are estimated to impact between about three percent of the general population.[10,38] Although considered a transient pediatric allergy, soybean allergy in adults is commonly comorbid with persistent peanut allergy and/or birch pollen allergy.[10] Similar to other food allergens, soy is found in a range of products, so allergy management consists of avoidance and carrying

epinephrine injectors.[38] The Food and Agriculture Organization (FAO) and World Health Organization (WHO) concluded that soybean allergy has medium-low potency with an eliciting dose of 40 to 60 mg.[10]

Soy is used in an abundance of foods and related products, such as fermented foods, Asian cuisine, infant formulas, protein alternatives, and other processed foods.[38] Interestingly, soy-allergic individuals typically can consume highly refined soybean oils and phospholipid-based, soy lecithin.[38] Despite soy allergy's low prevalence, the common use of soy-containing products in foods contribute to an emerging consumer concern about an increasing prevalence of soy allergy.[10] More soybean consumption is associated with higher prevalences of soybean allergies. For example, higher soybean consuming regions, like Eastern Asia, tend to have patients at risk for more severe allergic reactions.[10]

Allergic reactions to soy tend to cause mild skin, respiratory, gastrointestinal, and cardiovascular symptoms.[38] Like CMA and HEA, it is rare for anaphylactic shock to occur with soy allergies. However, reaction severity varies amongst individuals due to immunological differences impacting allergen potency.[38] Individuals who suffer from atopic dermatitis, peanut allergies, or birch pollen allergies are at a larger risk for developing soy allergy symptoms because of allergen cross-reactivity.[10] To diagnosis a soy allergy, an allergist can administer a skin-prick test, blood test, or histamine release assay to determine which food-specific IgE antibodies emerge upon soy consumption.[10,38]

Soy-based alternatives are commonly used for vegetarians and infants with lactose intolerance or CMA.[10] However, unlike CMA and HEA, the likelihood of developing soy allergy increases with early exposure.[10] Soy sensitization rates can impact up to eight percent of the

general population and have similar symptoms to soy allergic reactions.[10] With soy sensitization, undigested allergens are consumed and digested to be presented to antigen-presenting cells in the digestive mucosa to initiate immediate, IgE-mediated Th1 hypersensitivity reactions.[9] Primary sensitization emerges early in childhood upon Class 1 allergen consumption, such as soy ingestion.[10] Meanwhile, secondary sensitization emerges in adulthood from cross-reactivity, or primary sensitizing allergens and soybean homologue, Class 2 allergens.[10] In addition, occupational sensitization from a soybean processing facility can occur from respiratory aeroallergens like Gly m 1 and Gly m 2.[10]

The scientific nomenclature for soybeans is *Glycine max*, so soy allergen proteins are named according to the first three letters of the genus name, first letter of the species name, and with a number for order of discovery.[10] The WHO/International Union of Immunological Societies lists Gly m 1 through Gly m 8 as soybean allergens.[10] Soy allergens are classified into four categories based on storage protein globulin fractions, 7 S (B-conglycinin), 11 S (glycinin), 2 S, and 15 S.[10]

Gly m 1 and Gly m 2 are associated with severe occupational allergic reactions in soybean-sensitized individuals after inhalation of soybean allergens in a manufacturing workplace.[10] These occupational allergies are easily preventable for the general population, who consume peeled and processed forms of soy that do not expose consumers to Gly m 1 and Gly m 2 allergens.[10]

Gly m 4 is a PR-10 protein, like Bet v 1, and is abundant in mildly processed forms of soybean milk.[10] Gly m 4 contains various conformational epitope binding sites and heat-resistant, linear isoforms, which demonstrate why IgE production from Gly m 4 detection can deviate.[10]

Gly m 4 is associated with Class 2 allergens and secondary sensitization, because they are heat-resistant allergens recognized with oral exposure rather than gastrointestinal contact.[10]

Gly m 5 and Gly m 6, found in soy seeds, make up sixty percent of soy allergens and are associated with soybean-induced anaphylaxis.[10] Gly m 5 is a 7 S trimeric allergen with linear epitopes.[10] All three subunits of Gly m 5 have allergenic assets and have high resistance to food processing due to their heat-resistant, linear epitopes, like Gly m 6.[10] Meanwhile, Gly m 6 is an 11 S globulin allergen and is the most abundant soybean storage protein.[10]

Gly m 8 is a 2S albumin protein, which elicits soybean allergy with primary sensitization.[10] Similar to soluble allergens in wheat, albumin proteins are thermally stable and resistant to protease digestion.[10] Gly m 8 is a minor allergen because of its low allergenic potency and low cross-reactivity to other allergens.[10] However, IgE detection to Gly m 8 can provide insights for diagnosing soybean allergies in children, because of its low allergenic potency.[10]

Soy food processing is intended to alter protein structure and composition via denaturation and enzymatic hydrolysis, therefore reduced allergenicity is possible with heat, steam pressure, fermentation, and hydrostatic treatments.[10] For example, soy lecithin, a stabilizer, and emulsifier in food products, contains a variety of IgE binding soy allergens.[10] The method of refinement for refined soybean oil can impact whether allergens can bind to an antibody.[10] Unlike previously discussed allergens, heat and storage conditions can construct neo allergens and enhance soybean allergenicity.[10]

For soy, fermentation is the most capable method of improving food quality while limiting allergenicity.[9] During soymilk fermentation, lactic acid bacteria produce proteases to

hydrolyze soy proteins into peptides and free amino acids, which assists in soy allergen degradation.[9] Fermenting soymilk hydrolyzes Gly m 5 and Gly m 6 allergens, so fermentation assists in linear epitope destruction and reducing allergenicity.[9] In conclusion, fermentation reduces allergenicity to significantly hinder IgE-binding capability of digested allergens from fermented soymilk.[9]

Similarities amongst Legumes: Soybeans & Peanuts

Both soybeans and peanuts are legumes, so their similarity in structure and phylogenicity result in similar allergen structures amongst legumes.[10] This phenomenon explains why individuals allergic to peanuts may experience allergies to soy, because peanut-specific IgE antibodies can recognize homologous soybean allergens.[10] Homologous allergens are found in foods with similar phylogenicity, such as those in peanuts and soy. Homologous allergens cause cross-reactivity and IgE sensitization from two different allergens with similar epitope structures. For example, Gly m 5 is homologous to peanut allergen, Ara h 1, and both distinct allergens but known to induce similar IgE-mediated symptoms.[10] This is why individuals allergic to Gly m 5 may be co-sensitized to peanuts, because of the homology between Gly m 5 and Ara h 1.[10] Furthermore, Gly m 4 is homologous to Ara h 8, both of these allergens are prone to cross reactivity with birch tree pollen, related proteins like Bet v 1.[10] Cross-reactivity amongst soybeans and other allergens contributes to soy’s resistance to food processing and digestion.[10]

Peanut Allergy

In Western populations like the United States, Europe, and Australia, peanut allergies are on the rise, which is concerning due to peanuts’ association with highly variable symptoms

ranging from OAS to anaphylaxis.[39,40] Physical symptoms associated with peanut allergies include oral swelling, dizziness, decrease in blood pressure, and poor blood circulation.[40] Like a soy allergic reaction, these symptoms have a rapid onset, so epinephrine injections are recommended for emergency treatment to avoid life-threatening reactions.[40]

A multitude of factors contribute to the rapid rise in peanut allergies, specifically in developed, Western nations.[40] Developed nations have improved hygiene and sanitation, so children are not primed to infections at a young age. This lack of exposure prevents the immune system from developing and becoming capable of differentiating a harmless versus a harmful substance.[40] Approximately twenty percent of peanut allergies are attributed to the HLA-DR and DQ gene regions on a chromosome, which are not preventable.[40]

The scientific nomenclature for peanuts is *Arachis hypogaea* and it exists in two, immunologically similar subspecies: *A. hypogaea hypogaea* and *A. hypogaea fastigata*.[39] Linear epitopes are associated with peanut Class 1 allergens such as Ara h 1, Ara h 2, and Ara h 3.[39] Class 1 allergies emerge in children and resolve with the maturation of the gut microbiome; however, only twenty percent of peanut allergies resolve with age.[39] Meanwhile, Class 2 allergens are associated with heat-labile, conformational epitopes and their ability to bind IgE.[39]

Ninety percent of individuals with a peanut allergy undergo an immunological reaction when exposed to Ara h 1.[39] Ara h 1 is a peanut kernel protein with a linear epitope structure.[39,41] Ara h 1's allergenicity is associated with non-heat-treated peanut products, rather than those that have been boiled or fried.[41] Peanut allergy prevalence is on average lower in China than Western nations like the U.S. and U.K..[41] This phenomenon is a result of heat-treated peanuts being a common ingredient in Chinese cuisine and sauces.[41] For example, the Ara h 1 allergen is more

allergenic in an unprocessed peanut than a boiled peanut, whose IgE-binding capacity and epitope recognition changed with heat treatment.[41]

Ara h 2 is a major peanut allergen, which is a non-glycosylated, storage protein.[39] Ara h 2 is a Class 1 allergen and associated with more severe symptoms due to its resistant, linear epitope structure.[39] Ara h 2 maintains structural stability after heat treatments, the Maillard reaction, and human digestion.[39] This explains why IgE-reactivity becomes more severe with antibody-epitope affinity, therefore enhancing allergenicity.[39]

Ara h 6 and Ara h 2 have fifty-three percent identical primary sequences, and contain linear and conformational epitopes.[39] Both of these allergens are resistant to heat and digestion; in addition to cross-reactivity due to allergen structure similarities.[39] Despite maintaining stability to dry heat and the Maillard reaction, Ara h 6's allergenicity can be altered with wet-based treatments such as boiling or pasteurization, which cause allergen denaturation and/or aggregation.[39]

Peanut oral immunotherapy (POIT) has high success rates, specifically for those beginning treatments prior to preschool.[2] It is important to introduce infants to peanut-containing products at 4 to 6 months old, while waiting longer can increase the risk of developing a peanut allergy.[29] In the 2015 study, Learning Early About Peanut Allergy (LEAP), U.K. pediatricians questioned why Israeli pediatricians were less likely to diagnose infants and children with peanut allergies.[28] This study unveiled Israeli children were exposed to peanuts in their diets early on. For example, Bamba is a popular snack, it is a corn puff with highly processed, peanut powder; therefore, it contains low levels of peanut allergens to aid in building allergy tolerance.[28] In conclusion, the LEAP study demonstrated that early food diversification and building a tolerance

to peanut allergens was proactive in heavily reducing allergy emergence, in contrast to peanut avoidance.[28] The younger the individual, the more reactive their immune systems are to treatment interventions, which is demonstrated by building allergen tolerance and observing symptom responsiveness. [28]

Like soybeans, peanuts are found in a variety of unexpected foods and peanut-containing products, so extreme caution is necessary for allergic individuals.[40] Peanut oil is a highly refined product, so allergens are limited; however, foods that do not contain peanuts can become contaminated when exposed to peanuts during manufacturing or food preparation.[40] Unlike soy allergies, a peanut allergy can be mediated by a dose as small as 4 mg (about half the weight of a grain of table salt).[39]

Tree Nut Allergy

The six most common tree nut (TN) allergies are caused by allergens found in walnuts, almonds, hazelnuts, pecans, pistachios, and cashews.[42] Unlike legumes such as peanuts and soybeans, TN differ botanically and are not grown on the ground.[42] However, TN allergy symptoms resemble peanut and soybean allergies, such as anaphylaxis in severe reactions.[42] TN allergies are more life-threatening than peanut allergies, because eighteen to forty percent of anaphylaxis fatalities are associated with TN allergic reactions.[27] TN allergies can be managed with dietary restrictions, antihistamines, OIT, and epinephrine injectors.[27]

Unlike peanut allergies, TN allergies develop later at 36 months, instead of 14 months.[27] Individuals who develop a TN allergy at an early age experience primary allergies like IgE-mediated symptoms.[27] Meanwhile, adults are likely to experience secondary allergies like OAS-related symptoms, years after having a presumed tolerance to tree nuts.[27] Two percent of children

are diagnosed with a tree nut allergy, and fifty percent of those tend to develop allergies to multiple tree nuts.[42] Only nine percent of TN allergies resolve with age.[27] However, those who do not outgrow TN allergies can have elevated IgE levels, develop AD, and are allergic to multiple foods.[27] Heat treatment is known to reduce allergenicity to peanuts and wheat; however, tree nuts are heat-resistant and processing modifications fail to reduce their allergenicity.[21]

For the diagnosis of seed related and TN allergies, a Basophil Activation Test (BAT) is used to distinguish allergic from non-allergic individuals based on IgE reactivity to specific allergens in nuts and seeds.[27] BAT is an in vitro diagnostic tool that measures IgE antibody ability based on their capability to activate cells and trigger degranulation upon allergen exposure.[27] BAT has high specificity, so it can distinguish specific allergens found in cashews, hazelnuts, walnuts, sesame, and peanuts to distinguish allergic individuals.[27]

A double-blind, placebo-controlled oral food challenge would be the golden standard for diagnosing a TN allergy, which is a broad term for a variety of nuts.[27] During a double-blind, placebo-controlled OFC, increasing doses of a suspected tree nut are administered and neither the patient nor allergist know if an allergen or placebo is being consumed.[27] This test determines if an individual is sensitized or actually allergic to a suspected tree nut.[27]

Unlike CMA, HEA, and peanut allergy, OIT for TN allergies is a debatable topic.[27] In Canada, OIT is considered the standard treatment for desensitizing allergic individuals.[27] TN allergies significantly vary amongst geographical regions; for example, Europeans are most commonly allergic to hazelnuts, which are cross-reactive with aeroallergens in birch tree pollen.[27] Meanwhile, American TN allergies are most triggered by almonds, cashews, and walnuts.[27] Nine to fifteen percent of Americans allergic to TN are allergic to almonds, whose

symptoms are not immediate, and secondary sensitization is correlated with birch.[27] Asian countries have a significantly low prevalence of TN allergies compared to Western nations.[27] However, highly Westernized cultures in Asia, such as Hong Kong, are seeing rates of anaphylaxis-inducing TN allergies increase.[27]

Peanuts and tree nuts are commonly manufactured and processed in one facility, so doctors advise individuals with tree nut allergies to not consume peanuts due to the risk of cross-contact.[42] The highest incidence of cross-reactivity in TN occurs amongst those in the same botanical family, such as pecan-walnut and pistachio-cashew.[27] The phenomenon of cross-reactivity explains why eighty one percent of TN-allergic individuals cannot outgrow their TN allergies.[27] Tree nuts are found in unexpected products, such as cereal, pastries, candies, sauces, alcoholic beverages, and even cold cuts such as Mortadella.[42] Unlike peanut and soybean oils, tree nut oils are less refined and are used in cosmetic products, so application to the skin can trigger AD.[42]

Sesame Allergy

Sesame allergy tends to persist with age and its unpredictable symptoms ranging from mild hives to life-threatening anaphylaxis.[43,44] In the United States, approximately twenty-three hundredths of a percent of the general population suffer from a sesame seed allergy.[43] Similar to legume and nut allergens, sesame allergies differ amongst geographical region and cultures.[44] For example, in India, sesame allergy prevalence is low, and it is a common ingredient in Indian cuisine; therefore, it is hypothesized Indians built a tolerance to sesame allergens.[44] Meanwhile, sesame allergy is the third most prevalent food allergy in Israel, despite being a common

ingredient in Israeli cuisine.[44,45] In Israel, thirty percent of individuals allergic to sesame suffered an allergic reaction prior to one years old with anaphylaxis being the most common symptom.[45]

Sesame is an ingredient commonly found in breads, pastries, soups, oils, salad dressings, and tahini.[44] Similar to legumes and tree nuts, sesame is a "hidden" allergen as it is an ingredient inclusion in a variety of cuisine. It is vital for sesame-allergic individuals to check labelling and be informed of other names sesame might be listed under.[43] Under the FASTER Act of 2021, the United States mandates for the future production of apparent labelling of sesame and sesame-containing products after January 1, 2023.[43] This was a significant measure because sesame was previously an undisclosed ingredient under the ingredient list as a part of natural flavorings or added spices.[43] Unlike both peanut and soybean oils, sesame oil is unrefined and cold-pressed; these processing methods make distinct aromatics apparent and allow allergens to retain their allergenic structure.[43] Unlike peanut oils, sesame oil is not used for deep frying and is used as a finishing garnish because of its distinct, nutty, and toasty aromatics.[43]

Blood serum allergy testing is advised for those at risk of a sesame allergy, rather than a skin-prick test, to ensure there are no false-negative results.[44] Oleosin allergies requires blood serum testing due to oleosin's hydrophobic structure and inability to dissolve in diagnostic extracts.[44,46] Like allergenic proteins, lipids can mediate an allergy or immune response when attached to lipophilic proteins.[46] Oleosins are fat-soluble and vital for lipid structural integrity, they also hide oleosin-allergenic epitopes.[46] Oleosins are lipid, storage allergens found in peanuts (Ara h 10, Ara h 11, Ara h 14, and Ara h 15), hazelnuts (Cor a 12, Cor a 13, and Cor a 15), Tartarian buckwheat (Fag t 6), and sesame (Ses i 4 and Ses i 5).[46]

Like legumes and nuts, seeds, such as sesame and coconuts, evolved from plants, so they share common allergenic proteins.[44] This phenomenon explains why similar protein structures found within seeds and plants can cause co-positive allergy tests and cross-reactivity.[44] Sesame and coconuts allergies are common in those who have peanut and/or tree nut allergies due to similar allergenic protein structures.[45]

Fish Allergies

Fish allergies are IgE-mediated, and symptoms range from mild oral symptoms to life-threatening anaphylaxis.[47] The heat-resistant, strong allergenicity fish allergen, B-parvalbumin, triggers sensitization in ninety-five percent of fish allergic individuals.[47,48] Some individuals can have a fish allergy to collagen-derived, flesh and bone containing gelatin, which does not cross react with B-parvalbumin.[47,48]

Unlike milk and egg allergies, forty percent of individuals did not become allergic to fish until adulthood.[49] Fish allergies impact one percent of the global population, and are caused by the cross-reactive major allergen, B-parvalbumin.[47] Low B-parvalbumin levels are associated with migratory, dark-fleshed fish; meanwhile, high B-parvalbumin levels associated with sedentary, white-fleshed fish and rapid muscle relaxation.[47] The amount of B-parvalbumin present in a fish impacts its degree of allergenicity.[47] Fish allergies refer to those caused by B-parvalbumin allergens found in finned fish, like salmon, tuna, and cod.[49] Meanwhile, shellfish allergies are caused by heat-resistant, tropomyosin pan-allergens in crustaceans, mollusks, and house dust mites.[48,49]

Interestingly, tilapia contains tropomyosin and parvalbumin allergens, which is why it is common for individuals allergic to be allergic to both shellfish and finned fish.[48] Individuals with

fish allergies can be placed into three groups: poly-sensitized (allergic to all fish), mono-sensitized (selective allergies to one fish species), or oligo-sensitized (selective allergies to specific fishes).[48] This demonstrates that allergic individuals can react to only specific allergens found within fish and fish-containing products. For example, different variations of fish contain allergens aside from parvalbumin, such as shellfish contain tropomyosin, fish gels contain collagen, and fish eggs contain vitellogenin.[48]

Like other food allergies, a fish allergy diagnosis would be assessed using a skin-prick test or blood test, and treatment for fish allergies consists of avoidance and epinephrine injections.[49] Traditional fish OIT consists of chronic ingestion of fish, which can put patients at risk for heavy metal toxicity and food aversions.[47] A fish allergenicity ladder provides a scale for B-parvalbumin levels in several types of fish.[47] Catfish, grass carp, and tilapia are associated with the highest B- parvalbumin levels ; meanwhile, salmon, cod, and tuna are associated with lower allergenicity.[47] Novel fish OIT patients consume fish with increasing doses of parvalbumin to mitigate potential toxicity, differentiate between allergies and tolerance, and predict cross-reactivity.[47] In OIT, low allergenicity fish are primarily introduced and followed by fish with increasing doses of B-parvalbumin.[47] Fish egg allergies to vitellogenin are rare.[48] However, fish collagen allergies are moderately prevalent and impact populations who consume raw fish.[48]

Like seeds and nuts, fish can be considered a “hidden” allergy because it is found in unexpected products like imitation crab, cooking stock, Worchester sauce, and Caesar dressing.[49] Food preparations and food processing methods can alter fish allergenicity. For example, cooking, smoking, and brining can alter fish allergenicity by reducing parvalbumin levels via the Maillard reaction.[48] Despite altering and reducing parvalbumin, food processing cannot eliminate parvalbumin entirely.[48]

Shellfish Allergies

Shellfish allergies refer to IgE-mediated allergy symptoms that immediately emerge after consuming crustaceans and/or mollusks, which are invertebrate, marine animals with a hard exoskeleton.[50] Crustacean allergies are the most common shellfish allergy, which is caused by allergens found in crabs, lobsters, shrimp, and prawns.[50] Meanwhile mollusk allergens are found in squid, octopus, mussels, snails, clams, and oysters.[50]

The main allergen in shellfish is tropomyosin, a heat-resistant and genetically conserved, muscle protein that elicits IgE-mediated allergy symptoms.[51] Parvalbumin allergens in fish have no immunological overlap with tropomyosin found in shellfish.[52] Invertebrates like crustaceans, mollusks, insects, and arachnids contain pan-allergenic tropomyosin, a conserved allergen structure that is associated with cross-reactivity and IgE-mediated allergies.[53] Some specific examples of tropomyosin-containing insects are house dust mites and cockroaches.[52]

The high degree of genetic sequence and cross-reactivities amongst different crustaceans has led researchers to hypothesize tropomyosin to be the shellfish allergen with the most widespread impact.[53] PCR amplifies DNA markers to detect heat-resistant allergens in distinct species of crustaceans with similar, conserved genetic sequences.[51] The genetic similarites associated with tropomyosin-containing organisms is why allergies to any mollusk or crustacean, whether it is shrimp, lobster, or crab, are classified under the broad term, shellfish.[51]

Thermal processing in the forms of baking, boiling, and frying alter allergen structure, which slightly diminishes allergenicity.[51] Thermal processing does not eliminate the impact of shellfish allergens, because the immune system continues to recognize and elicit an IgE response upon exposure to tropomyosin allergens.[51] When immunoproteins bind to calcium ions, IgE

antibody confirmations change to sensitize allergies, which demonstrates processing does not eliminate allergens.[22] When calcium ions detach from tropomyosin, allergens unfold and cannot bind IgE antibodies, which reduces allergenicity.[22]

Heat-resistant, membrane calcium proteins (SCP) found in crustaceans, mollusks, and insects can trigger mast cells, which will signal histamine release and cause inflammatory symptoms.[51] Symptoms associated with SCP sensitized individuals resemble an allergic reaction, even if tropomyosin is not present.[22] This phenomenon demonstrates why improper food processing is a hazard, even in highly processed foods.[22]

Meanwhile, calcium-depleted proteins are hypoallergenic and can be used in assisting with desensitization and oral food challenges.[22] Enzymatic hydrolysis demonstrates the most potential in diminishing allergenicity enough to reduce the severity of IgE-mediated symptoms.[51] In addition, acid hydrolysis can reduce but not eliminate allergenic proteins in crustaceans.[1] Likewise, the Maillard reaction's glycation reduces shrimp tropomyosin from binding with IgE to mediated a reaction.[54] Since heat treatment and processing cannot eliminate allergens in shrimp, genetic modification has been sought as a solution to formulate non-allergenic shrimp, who lack tropomyosin.[51]

Shellfish allergies most commonly emerge in adulthood and are associated with severe symptoms, such as life-threatening anaphylaxis.[50] Individuals with asthma, extreme shellfish sensitivity, other food allergies, and family members with shellfish allergies are at the highest risk for developing shellfish allergies.[50] Like most food allergy diagnoses, a shellfish allergy diagnosis consists of skin-prick tests and blood serum tests.[50] If these results are inconclusive, an oral food challenge will be assessed to measure sensitivity to shellfish.[50]

Shellfish consumption avoidance and carrying an epinephrine injector are necessary safety precautions for those with shellfish allergies.[50] When dining out at restaurants, especially seafood restaurants, it is important to ensure there has been no cross-contamination in cooking pans, frying oils, or utensils, because even trace amounts of shellfish allergens can be lethal.[50] Shellfish is found in ingredients like cooking stock, but it must be explicitly listed on the ingredient label.[50] Meanwhile, mollusk-containing items do not require explicit listing.[50]

Conclusion: Current Research & Future Needs

Current Research

Some food allergens are not structurally labile, so their confirmation can be simply altered upon heat treatment or human digestion. These transient allergens include cow milk, hen egg, wheat, and soy, which are known to disappear with age.[2] These allergens are associated with confirmational epitopes, which trigger an allergic reaction based on allergen 3-D shape.[8] When a secondary, tertiary, or quaternary allergenic protein unfolds and denatures from food processing, the potential of an allergy trigger disappears.[8]

Building allergen tolerance is easier to do for foods that contain heat-labile epitopes, because OIT can expose patients to denatured, baked versions of food allergens. This method of exposure primes the immune system to recognize allergens and build a tolerance without triggering an IgE-mediated allergic reaction.[8,13] Foods like wheat-containing items, cow milk, and hen egg are baking ingredients, whose allergenicity is drastically reduced after being baked in a pastry matrix.[8] In milks, such as dairy and soy, fermentation and enzymatic hydrolysis are common methods for reducing allergenicity by deconstructing allergens into unrecognizable peptides, which will not trigger an allergic reaction.[9] It is important to use OIT for children with developing immune systems and gut mucosa. Younger immune systems can change from a Th2 response to a Th1 response, which tolerates allergens and stops the body from misidentification.[11,29,30]

Meanwhile, other food allergens persist or begin in adulthood; those allergies do not respond effectively to OIT due to heat-resistant and digestion-resistant allergen structures.[8]

These food allergens include peanuts, tree nuts, sesame, fish, and shellfish.[2] Structurally stable allergens contain linear epitopes, which is a simple, stagnant amino acid sequence capable of triggering an allergic reaction whether it is denatured or not.[13] Linear epitopes, such as Ara h 2 in peanuts, have chemical structures that mitigate allergenicity changes from food processing, like internal disulfide bonds which function like steel bridges.[8,39] Allergens that have structural features such as linear epitopes, glycosylation, and disulfide bonds tend to maintain allergenicity after enzymatic digestion and thermal heat treatment, even in foods that are associated with diminishing allergies.[8] For example, Gal d 1 in hen eggs is heat-resistant and moderately digestible, which is why it is a major egg allergen and is difficult to build a tolerance with OIT.[8,29] In foods like crustaceans and peanuts, the Maillard reaction in cooking can enhance allergenicity with creation of neo allergens, which are highly detectable by IgE antibodies.[39,54]

Oral immunotherapy is the golden standard for desensitizing individuals to food allergens, because it builds an immunologic tolerance with escalating, allergen doses.[29] In 2024, the FDA approved the anti-IgE injection, Omalizumab, to be used with oral immunotherapy.[31,32] This injection allows patients in oral immunotherapy to take in IgE antibodies, so higher allergen doses with fewer symptoms can occur in the future.[31,32]

Future Needs

Current research is moving away from treating a singular allergy and shifting towards multi-allergy treatments to desensitize patients to a variety of allergens at once. Multi-allergy treatments include subcutaneous immunotherapy (SCIT) environmental allergen injections and immediate relief injections, like Omalizumab.[31] SCIT is a treatment for food allergies and OAS, since food allergens cross-react with environmental allergens, such as tree nuts and soybeans with birch trees.[27,31]

A parvalbumin concentration ladder was created for individuals allergic to fish, so they can consume low allergenicity fish, increase their allergen doses, and build a tolerance.[47] Creating allergen concentration ladders for each of the "Big Nine" Food Allergens could assist in constructing a cost-effective, universal protocol for proper allergen introduction.[47]

A malfunctioning immune system is the root of systemic, allergic diseases such as atopic dermatitis, asthma, rhinitis, and food allergies.[55] Allergy pathogenesis is multifaceted and can be attributed to maternal microbiome, microecology, food introduction times, genetics, epigenetics, and individual immunity.[55] Epigenetics impact genetic expression without altering DNA sequence.[55] For example, DNA methylation can be used to distinguish allergic from healthy individuals, because a methyl group is added to the transcription start site, which can alter genetic repression or expression.[55] Epigenetics depict the phenomenon of environmental factors, such as drug-use or exposure to pollution, altering genetics, such as allergic disease's impact on DNA methylation, post-translational histone modifications, or non-coding RNA.[55] More research is being done on how epigenetics contributes to the persistence of heat-labile allergies, because it does not make sense for some to build immunotolerance and others to not.[55]

Skin-prick and IgE blood serum tests can only diagnose IgE-mediated symptoms, so food sensitivities cannot be accounted for.[25] Skin-prick tests can provide false-negatives, so diagnostics are shifting towards component-resolved diagnostics (CRD).[56] CRD informs patients on which allergens and amounts elicit individual allergic reactions.[56] CRD can be performed by a singleplex or multiplex assay, which both use previous findings to determine which antibodies emerge upon allergen exposure.[56] CRD distinguishes true allergies from cross-reactive symptoms.[56] Cross-reactive, environmental allergens biochemically resemble food allergens and elicit reactions after primary sensitization to the food allergen, which is why cross-reactive allergens elicit milder symptoms.[56] Researchers in the U.S. are seeking to genetically modify allergen containing foods to be allergen poor, or even allergen-free.[39]

In conclusion, the outcome of having a "Big Nine" food allergy demonstrates the interconnectedness of allergen protein stability and its impact on individual immunity. Primarily, when allergies were researched, strict avoidance of allergens was recommended. However, with current research, active intervention is the newest recommendation using treatments like oral immunotherapy and biologic injections, like Omalizumab. These contemporary treatment methods do not target the prevention of allergic reactions but rather seek desensitization and allergen tolerance. The goal of building allergen tolerance to the "Big Nine" is to reduce the risk of life-threatening anaphylaxis and to uplift the burden of fearing allergen-containing food products. Although there is no established method to entirely cure allergies, the global, growing understanding of epitope structure and allergen heat-stability has assisted researchers in constructing solutions to understanding and managing life-long, persisting allergies.

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