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Food allergy in children-The current status and the way forward

Elghoudi *et al.* Food allergy in Children

Abstract

Food allergy in children is a major health concern and its prevalence is rising. It is often over-diagnosed by parents, resulting occasionally in unnecessary exclusion of some important food. It also causes stress, anxiety and even depression in parents and affects the family's quality of life. Current diagnostic tests are useful when interpreted in the context of the clinical history, although cross-sensitivity and inability to predict the severity of the allergic reactions remain major limitations. Although oral food challenge is the current gold standard for making the diagnosis, it is only available to a small number of patients because of its requirement in time and medical personnel. New diagnostic methods have recently emerged, such as the Component Resolved Diagnostics and the Basophil Activation Test, but their use is still limited and the latter lacks standardization. Currently, there is no definite treatment available to induce life-long natural tolerance and cure for food allergy. Presently available treatments only aim to decrease the occurrence of anaphylaxis by enabling the child to tolerate small amounts of the offending food, usually taken by accident. New evidence supports the early introduction of the allergenic food to infants to decrease the incidence of food allergy. If standardised and widely implemented, this may result in decreasing the prevalence of food allergy.

Key Words: Oral food challenge; Oral immunotherapy; Allergens; Anaphylaxis; Desensitization; Immunoglobulin E; Eosinophilic gastrointestinal diseases; Histamine; Mast cells; Basophil activation test

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Core Tip: Food allergy in children is a potentially serious condition with an increasing prevalence. Current diagnostic tests are useful when interpreted in the context of the clinical history. The oral food challenge is the current gold standard for making the

diagnosis, but its use is limited. New diagnostic methods have recently emerged. Currently, there is no definite treatment to induce life-long natural tolerance and cure for this condition and available treatments only aim to decrease the occurrence of anaphylaxis. New evidence supports the early introduction of the allergenic food to infants to decrease the incidence of food allergy.

INTRODUCTION

Reactions to foods, including allergies, have been known for many centuries. “What is food to one man may be fierce poison to others”, was quoted by Lucretius (99-55 BC). In the 1920s and 30s, food intolerance was blamed for many disorders and became a common concern amongst parents in the 1980’s. Not surprisingly, it was associated with a steady increase in the diagnosis of food allergies^[1]. This was caused by an increase in the prevalence of atopic conditions as a result of different environmental and genetic factors and also by an increase in public awareness. Immunoglobulin (IgE)-mediated food allergy is a global health concern that affects millions of individuals, disrupting many aspects of their lives^[2,3].

The condition may cause stress, fear, anxiety in affected children and their parents alike. It also negatively impacts the nutritional status of children with either proven or merely suspected food allergy by resulting in food restriction, elimination, or complete avoidance of particular important food. Stigma, bullying at school, regulation from normal social life, such as attending parties and dining out, also have a significant impact on the child and the family. As for parents, holiday planning becomes a nightmare, similar to when the child goes to school for the first time or moves to a university campus and becomes independent.

The worldwide prevalence of food allergy is estimated to be around 4% of children and 1% of adults, with an increased prevalence in the past two decades^[2,4,5]. Differences in reported prevalence are because food allergy is not fully understood, and some of the adverse reactions to food are not allergic. Although in the Western world it is believed that approximately 25% of adults suffer from a food allergy, when accurately diagnosed

by testing and oral food challenge (OFC), its true prevalence is found to be much lower, closer to 8% in young children and less than 4% in adults.

This review will revisit the definition, prevalence, and clinical presentation and evaluate the current management of food allergies in children, focusing essentially on the most common IgE-mediated food allergy.

DEFINITION

Different terminologies in food allergy are a source of confusion, with terms such as allergy, hypersensitivity, pseudo-allergy, and intolerance often being incorrectly used interchangeably. At first, a food allergy may sound to parents, and even some professionals, like a single simple disease. However, in reality, it is far more complex.

Adverse reactions to food are defined as an abnormal response related to the ingestion of that food. They can be classified as food intolerance or food allergy based on the pathophysiological mechanism of the reaction^[6]. The vast majority of food allergic reactions reported by parents and the general population are, in fact, food intolerances.

The most acceptable and widely used definition of food allergy states that it is an adverse immune response to food proteins that occurs in a susceptible host^[2]. Its manifestations are not dose-dependent but are reproducible^[6]. Furthermore, food allergy is not one single distinct condition but a spectrum of clinicopathological disorders^[7]. In addition to the classic fast (IgE-mediated) food allergy, other Type 1 hypersensitivity diseases cover medical problems such as acute allergic hives, allergic gastrointestinal diseases gut, e.g., eosinophilic esophagitis, an acute flare-up of eczema, and oral food pollen syndrome.

As a result, the manifestations of food allergy are very broad and entirely depend on the underlying immune mechanism involved and on the affected target organ(s), resulting in a wide spectrum of manifestations commonly involving, alone or in combination, the skin, the respiratory and cardiovascular systems. Thus, diagnostic tools for food allergy, such as the skin prick test and the specific IgE test, have limitations caused by cross-reactivity and the inability to predict the severity of the allergic reaction;

their results must, therefore, always be interpreted in the context of the clinical symptoms to make an accurate disease assessment and, hence, a diagnosis.

In contrast to food allergy, food intolerance is defined as a non-immune reaction to food^[2]. It encompasses adverse responses to food, caused by the inherent properties of that particular food (*i.e.*, contamination with a toxin or pathogen, presence of a pharmacologically active component such as caffeine, alcohol, monosodium glutamate), or more commonly caused by an abnormal response of the host, for instance, enzyme deficiencies such as lactase (lactose intolerance), or metabolic disorders (galactosemia, congenital fructose intolerance), or food aversion (due to psychological issues). The clinical manifestations tend to be dose-dependent and are not consistently reproducible.

EPIDEMIOLOGY

Accurate ascertainment of the prevalence of food allergy facilitates the planning of allergy services. Unfortunately, accurate prevalence statistics are notoriously difficult to obtain. The reasons include the existence of various definitions and methods of reporting food allergy and the pleiomorphic manifestations of food allergy with various degrees of severity. In addition, some reports may have also included confounding factors by either investigating specific populations, focusing on specific foods, or using different methodologies. Furthermore, ³there are wide geographic variations, diet exposures, differences according to age, race, ethnicity, and many other factors. Additionally, the presence of multiple food allergies in children is not often accounted for in prevalence studies.

Methods of reporting food allergy

The methods of reporting food allergy, either self-reported by the individual child, parents, or even by adult patients, lead to different prevalence estimates, as ³self-reported food allergy rates are notoriously higher than those confirmed by medically supervised OFCs^[8].

Offending food and geographical variations

Food allergies disproportionately affect persons in industrialised or Western countries and are more common in children than adults. There is a relatively short list of foods that account for the majority of the more serious manifestations of food allergy, namely peanut, tree nuts, fish, shellfish, egg, milk, wheat, soy, and seeds^[4,9,10]. A survey by the World Allergy Organization of 89 member countries using widely different methodologies reported wide variations in prevalence data revealing that prevalence rates for those < 5 years of age were lowest in Thailand and Iceland and highest in Canada, Finland, and Australia^[11]. A birth cohort study from 9 European countries where 12049 infants were followed until the age two years, and using OFC to confirm the diagnosis of food allergy, found an adjusted mean incidence of egg allergy of 1.23% (95%CI, 0.98% to 1.51%), with the highest rate in the United Kingdom (2.18%) and the lowest in Greece (0.07%)^[12]. However, the prevalence rates of milk allergy were lower (0.54%; 95%CI, 0.41% to 0.70%), with the highest rates in The Netherlands and United Kingdom (1%) and the lowest rates in Lithuania, Germany, and Greece (< 0.3%)^[12,13].

In a meta-analysis of food allergy by history alone, the prevalence of fish allergy was 0%-7% and shellfish allergy 0%-10.3%, whereas, when food challenges were used instead for the definition, the prevalence of fish allergy (0% to 0.3%) was similar worldwide, with shellfish allergy prevalence (0% to 0.9%) being higher in the Southeast Asia region^[14]. A systematic review and meta-analysis of 36 studies from Europe and the United States on the prevalence of tree nut allergy showed a prevalence rate < 2% for oral challenge confirmed allergy and 0.05% to 4.9% for possible allergy. Hazelnut was the most common tree nut allergy in Europe, and walnut and cashew were the most common in the United States^[15]. Some of the highest rates of food allergy, diagnosed by an OFC, were reported from Australia, where > 10% of one-year-old infants had challenge-proven IgE-mediated food allergy to one of the common allergenic foods of infancy. The prevalence of any sensitisation to peanut was 8.9% (95%CI, 7.9-10.0); raw egg white, 16.5% (95%CI, 15.1-17.9); sesame, 2.5% (95%CI, 2.0-3.1); cow's milk, 5.6% (95%CI, 3.2-8.0); and shellfish, 0.9% (95%CI, 0.6-1.5). The prevalence of challenge-proven peanut allergy was 3.0% (95%CI,

⁸ 2.4-3.8); raw egg allergy, 8.9% (95% CI, 7.8-10.0); and sesame allergy, 0.8% (95% CI, 0.5-1.1)^[16,17].

Ethnicity

A systematic review aiming to address potential racial and ethnic disparities showed that black persons, mainly children, had increased food sensitisation or food allergy. However, these results were tempered by the heterogeneity of the different reports and also by some inherent limitations of some of the included studies^[18]. The ³ rate of increase in self-reported paediatric food allergy was greater in non-Hispanic black subjects (2.1% per decade) compared with non-Hispanic white subjects (1% per decade)^[19]. In a high-risk inner-city cohort of children, ⁶ 74% black and 18% Hispanic, a very high rate of food allergy (9.9%) was reported^[20]. African American children have higher odds than white children of having an allergy to wheat, soy, corn, fish, and shellfish. However, they had similar rates of peanut, milk, and egg allergy; and lower rates of tree nut allergy, but they also had higher rates of anaphylaxis and emergency department visits^[21]. In the United Kingdom, between 1990 and 2004, there was an increase, from 26.8% to 50.3%, in the proportion of non-white patients with peanut allergy (but not egg allergy). However, the proportion of black subjects attending the clinic had not changed during that period^[22]. In New York City schools, no difference was found in food allergy rates between black and white children^[23].

Multiple food allergies

An electronic household survey in the USA estimated ¹⁴ that 8% of children have a food allergy, with ⁶ 2.4% having multiple food allergies and 3% having experienced severe reactions^[5].

It is, therefore, clear that different reports of prevalence are influenced by many factors, alone or in combination, such as race, ethnicity, country, geographical location, and offending allergens, as well as many other factors such as parents' education, development of health care and the reporting systems. Therefore, disparities ⁶ need to be

better characterized. They might reflect differing awareness of food allergy and access to health care, racial/ethnic or socioeconomic influences on childhood feeding practices, or true differences in prevalence^[24].

PATHOPHYSIOLOGY AND MEDIATORS OF FOOD ALLERGY

⁵ The immune system plays an integral role in maintaining tolerance to innocuous antigens.

The primary exposure

⁹ IgE-mediated food allergies occur as a result of dysregulation in the immune system, that maintains a state of tolerance by preventing benign food antigens from being incorrectly identified as pathogens. Oral tolerance to foods is defined as the trans-mucosal crossing of food antigens, processing by non-activated dendritic cells and the Control of the inhibitory cytokines mediators as interleukin (IL) 10, by the cells taking the first role in the primary allergen exposure where the unknown protein particles taken by antigen-presenting cells to the lymphoid tissue proximal to the site of exposure. Usually, the process gives the all-clear to the new food protein through T regulatory cells and inhibiting Th2 cells production. It will also result in increased IgA and IgG₄ production with a decrease in IgE production. In addition, there is also an immune suppression of eosinophils, basophils, and mast cells effector cells responsible for causing symptoms. In such a scenario, the innocent food protein will be given the “all clear” by default by the balanced and non-incorrectly triggered immune system.

Sensitisation is defined when food-specific IgE is detectable in the blood. This immunological response is fundamental in the development of type 1 hypersensitivity reaction and it is primed by the transfer of food protein across the deranged digestive tract membrane and leads to an unnecessary release of inflammatory cytokines, which activate dendritic cells, which will, in turn, trigger naïve T cells into acquiring a Th2 phenotype. The latter will, ⁵ in turn, promote inflammatory signals which induce food antigen-specific B cells to produce food antigen-specific IgE. Sensitization, therefore, is

the mistaken identification of a benign food antigen as a pathogen. The specific IgE to that particular protein binds to the surface receptors of mast cells, basophils, macrophages, and other antigen-presenting cells, priming the immune system to an allergic reaction should a second exposure occur to that specific allergen.

A second exposure to the allergen results in the burst of mast cells, leading to the release of histamine, which is one of the most important preformed mediators responsible for the symptomatology of both mild allergic reactions and anaphylaxis. When histamine is secreted from mast cells and resemblance cells, its effect immediately manifests through fades within a few minutes. Histamine causes all the signs and symptoms seen in mild and severe allergic reactions such as increased capillary leak, hives, tachycardia, drop in blood pressure.

Other inflammatory mediators such as prostaglandin D₂, platelet-activating factor, and leukotrienes also contribute to the allergic reaction.

In summary, the five components of the immune system, the epithelium, innate immune cells, T cells, B cells, and effector cells (mast cells, eosinophils, and basophils), can either promote tolerance to food antigens or sensitisation to them, which will then lead to allergic manifestations.

The role of Epithelial Barriers

The role of the intestinal epithelial cells in the central regulatory mechanism controlling the absorption of ingested antigens is important. It helps maintain tolerance by preventing the unnecessary entry of antigens and thus avoiding the secondary production of inflammatory cytokines.

Antigens cannot freely pass an intact epithelial barrier but are often transported through mechanisms of net movement of particles present beneath the cells through several very specialized cells^[25].

In the absence of pro-inflammatory or danger signals, food antigens recognised by specialised antigen-presenting cells will further promote the maintenance of tolerance

through the release of mediators such as IL 10 and transforming growth factor-beta (TGF- β), which will promote the development of regulatory T cells^[26-28].

The role of T Cells

The relevant cytokine and other mediators released by a nonspecific line of defense cells such as natural killer cells, macrophages, neutrophils, mast cells, dendritic cells, mast cells, and basophils all help by playing a role in tolerance production and the generation of T regulatory cells^[26-28]. Moreover, products from the dendritic cells permit a complicated exchange process in the gastrointestinal lining to produce an inhibitory effect by binding the effector particles to CTLA-4^[29,30]. In addition, inflammatory mediators such as IL-10 released T regulatory cells can also have an inhibitory effect on effector cells^[31]. Th2 cells periodically move from the local lymphoid glands into the thin layer lining of the exposed surface of the gastrointestinal tract, where inflammatory mediators such as IL5 and IL13 stimulate the process of B cell activation, leading to the development of the body action towards certain foods. At the same time, naïve T cells transform into helper -and the release of IL-9, which eventually result in the development of allergic reaction and an increase in the histamine secreting cells^[32].

TYPES OF FOOD ALLERGY

10 Oral tolerance refers to a systemic immune non-responsiveness to antigens first encountered by the oral route. A failure to develop this homeostatic process in persons who are genetically and probably environmentally predisposed to atopy can result in the development of food allergy^[33]. Based on the immunological mechanism involved, food allergies may be classified into three types^[1-3,7,34,35].

IgE-mediated food allergy

This is the best-known and well-characterised type of food allergy. It is the most common food allergy in the Western world, with the highest prevalence in children below three

years of age (6%-8%)^[6]. There has been a steady increase in this type of food allergy and food induced-anaphylaxis in the Western world^[36,37].

These allergic reactions are immediate, reproducible, and caused by food-specific IgE, which can usually be detected by *in vivo* or *in vitro* tests to confirm the food allergy diagnosis^[6]. These food-specific IgEs bind to high-affinity receptors for the Fc region of IgE (FcεRI) on basophils, mast cells, dendritic cells, and Langerhans cells in the gut, skin, or through the respiratory system. When exposed to the offending food, the specific food antigen is recognised by two or more specific IgE bound to the FcεRI, resulting in a crosslink of the receptor and activation of mast-cells to release histamine and other mediators. These released chemical mediators will cause vasodilation, hives, angioedema, low blood pressure, and/or smooth muscle constriction, and consequent bronchospasm, diarrhoea, and vomiting^[38].

Food allergy-associated anaphylaxis is an IgE-mediated reaction. In a previously sensitised person with food-specific IgE on mast cells and basophils, the food allergen is ingested and absorbed into the local tissue, then cross-links with IgE resulting in immediate release of preformed mediators^[2,39,40]. This immune response is rapid; the onset of symptoms typically occurs within 5 to 60 min after exposure to the food. An anaphylactic reaction affects multiple organ systems and may rapidly develop severe symptoms (*e.g.*, hypotension or respiratory collapse) and even death^[41].

Although cutaneous manifestations such as hives and pruritus are the most common, they are absent in 20% of anaphylaxis persons. Thus, a high index of suspicion is required when other signs and symptoms such as cough, wheezing, laryngeal oedema, vomiting, diarrhoea, and hypotension are present. IgE-mediated food allergy is often associated with fatal anaphylaxis in children and adolescents. Recent data have linked cow's milk protein to several severe anaphylactic reactions, including a deadly anaphylactic reaction to baked milk following an OFC test.

Several devastating incidence of food allergy which unfortunately results in fatality either at take away restaurants, school or even following supervised food challenges

made the issue of food allergy a major concern for parents, public, school, and health authorities.

Up to one-third of the population now believes that they have food allergies, a much higher estimate than the actual prevalence based on physician diagnosis (5% of adults and 8% of children)^[42].

The most common foods incriminated in IgE mediated food allergy are milk, egg, peanuts, tree nuts, seafood, soy, wheat, and seeds. Sesame has recently been emerging as a typical new food allergen in the Middle East and Europe^[43].

Food pollen syndrome or Oral allergy syndrome: A unique and interesting form of IgE-mediated food allergy is a pollen-associated type of food allergy due to the cross-reactivity of epitopes shared between allergen molecules in certain pollens and some vegetables and fruits^[44]. Here, the primary sensitisation occurs to pollen allergen, with the initial symptoms being allergic rhinitis. However, upon further exposure to that particular fruit or vegetable which shares epitopes or components with pollens responsible for the primary sensitisation, other symptoms then develop such as allergic rhino-conjunctivitis, itching, redness and oedema of the lips, numbness in lips and tongue, itching, and swelling in the throat^[44,45]. Pollen food syndrome (PFS) usually does not lead to anaphylaxis, and its symptoms can usually be avoided by either peeling the skin of the fruit or vegetables or by boiling them. Rinsing the mouth with water usually eases the symptoms. PFS is commonly misdiagnosed as a true food allergy, with children being prescribed unnecessarily an adrenaline autoinjector^[46,47].

Non-IgE food allergy

These are immunologic reactions to food that occur without demonstrable food-specific IgE antibodies in the skin or the serum and can, therefore, have several pathogenic mechanisms^[48]. The non-IgE-mediated disease consists of a wide range of gastrointestinal conditions, generally of slow onset and with signs and symptoms very similar to other

common conditions, especially in the first year of life, such as colic, gastroesophageal reflux, diarrhoea, and eczema, making it difficult to recognise.

This type of food allergy has been increasing worldwide. It encompasses eosinophilic oesophagitis (EoE), Non-EoE eosinophilic gastrointestinal disorders (Non-EoE-EGID), food protein-induced enterocolitis (FPIES), and food protein induced allergic proctocolitis (FPIAP). While EoE, Non-EoE-EGID, FPIAP are chronic, FPIES is always an acute disease. Although T cells may play a central role in non-IgE mediated food allergy and EoE, the pathogenesis of FPIES and FPIAP remains less clear^[49,50]. Non-IgE mediated food allergies are usually managed by joint care between the paediatric allergist and the gastroenterologist.

Mixed IgE-cell-mediated food allergy

This occurs when both IgE and immune cells are involved in the reaction. Mixed and non-IgE-mediated food allergies, such as EoE, eosinophilic gastroenteritis (EG), and atopic dermatitis (AD), have a more prolonged onset and manifest primarily in the gastrointestinal tract and skin^[51]. Infants and young children with EoE may present with feeding dysfunction and failure to thrive, whereas older children and adults often manifest vomiting, abdominal pain, dysphagia, and food impaction. EoE is diagnosed by oesophageal biopsy, demonstrating the presence of > 15 eosinophils per high-powered field. It is not uncommon in patients with EoE to have other allergic diseases, such as allergic rhinitis and IgE-mediated food allergy. Food allergens and possibly aeroallergens seem to play causative roles in the immunopathology of EoE, and food-avoidance diets are often effective in inducing clinical and histologic improvement. When eosinophils are found distal to the oesophagus in the gastrointestinal tract, the diagnosis of EG is then made. Symptoms of EG vary depending on the portion of the gastrointestinal tract involved and may include abdominal pain, nausea, diarrhoea, malabsorption, and weight loss. Unlike EoE, food-avoidance diets offer little or no benefit in EG^[52].

AD also has features of mixed IgE- and non-IgE-mediated food allergy immunopathology. The presentation includes a chronic pruritic rash distributed on flexor

surfaces such as the antecubital and popliteal fossa, wrists, ankles, and neck. In approximately 35% of children with AD (typically young children with severe AD), food allergens may exacerbate their rash, causing increasing erythema and pruritus over a few hours if only IgE-mediated or over days if non-IgE mediated. Milk, soy, egg, wheat, and peanut are the most common culprit foods. Elimination of suspect foods often improves AD symptoms within a few weeks, whereas repeated exposure exacerbates symptoms^[52].

Sensitivity to food chemicals: This is thought not to be a true allergy and is not immune-mediated. However, it is commonly described in food allergy as it shares similarities with the latter. It represents an adverse chemical reaction to either usually existing food chemicals such as amines, salicylates, natural food colourings, and glutamate, or artificially added food chemicals such as sulfites, benzoates, and artificial food colourings. A small amount of these chemicals are well tolerated most of the time. Salicylates naturally exist in fruits, vegetables, nuts, and cereals and are also used to manufacture chewing gum, toothpaste, and mouthwashes. Amines such as histamine can occur naturally in food or are secondary to microbial contamination or fermentation. Histamine-associated symptoms include urticaria, angioedema, itching, rhinitis, conjunctivitis, abdominal cramps, palpitation, flushing, and headache^[53]. Glutamate is an essential amino acid occurring naturally in many foods such as cheese, tomato, mushrooms, soy, and yeast extract. Monosodium glutamate MSG (E621) is commonly used in the manufacture of soaps, food and sauces widely consumed in Asian restaurants. The “Chinese Restaurant Syndrome” is a condition caused by glutamate, widely used in Chinese food, and which manifests as headache, muscle tightness, nausea, tingling, flushing, and chest tightness.

A food additive is any substance not naturally present in that food, such as E 220, E 221, E 222 cited on some food labels. Sulfite is a very common food additive that exists in shrimps, beer, wine, dried grapes, and pizza dough and which may induce symptoms ranging from mild reactions to anaphylaxis. Food colourings can be found in tea, berries, and cinnamon, and, although they cause concern to the public, they rarely produce

reactions. The exact mechanism of producing these reactions is not fully understood. Colourings have also been linked to hyperactivity in children, especially when combined with other food additives^[54].

MANIFESTATIONS OF FOOD ALLERGY

We will focus exclusively on IgE-mediated food allergy, a type I hypersensitivity reaction that occurs when ingestion of specific food triggers a response by preformed circulating IgE antibodies developed earlier against that same food^[7,55].

When food molecules which have been wrongly appreciated as a pathogen in the atopic child, comes in contact with the lamina propria of the intestinal tract, it rapidly binds to basophils and mast cells, resulting in degranulation of these cells and the release of the inflammatory mediators such as histamine and tryptase^[56]. These mediators are responsible for the signs and symptoms are seen in mild and severe food allergic reactions such as the development of urticarial rash, hives, cough, hoarseness of voice, bronchospasm, hypotension, or collapse^[57,58].

Cutaneous manifestations

They are the most common IgE-mediated food-allergic symptoms. Usually presents as redness of the skin, itchy rash, which commonly takes the form of papules or hives. When the inflammation involves the deeper layers of the skin, the skin manifestation is called angioedema. Hives can last for hours if not treated. Angioedema develops when the swelling extends below the skin's surface and fatty tissue. It usually presents as eyelids, face, and/or lip swelling, causing significant discomfort. Eczema may develop or worsen in non-IgE-mediated food allergy, although pre-existing eczema can also worsen with IgE-mediated food allergy. The magnitude of the skin reactions in type 1 hypersensitivity food allergy is reflected by the surface area of the skin affected^[59].

Respiratory manifestations

The entire respiratory tract from the nose to the lungs can be affected. Symptoms vary from runny nose, congested nose, sneezing, itchy nose to cough, stridor, wheeze, or breathing difficulty. Some children experience severe tightness in the throat and a feeling of impending death^[7,58,60]. It has been reported that some patients who presented to the emergency room with anaphylaxis due to food allergy have been mistakenly diagnosed and treated as life-threatening asthma.

Gastrointestinal manifestations

Abdominal pain, vomiting, and diarrhea are the cardinal gastrointestinal feature of IgE-mediated food-allergic reactions. These symptoms are usually quick in onset and could appear immediately following the exposure to the offending food up to 2 to 4 hours later. Other problems such as constipation and failure to thrive are more common in non-IgE-mediated food allergy^[7].

Cardiovascular and neurological manifestations

They are usually described as the most severe complications of IgE mediated food allergy. Children become pale dizzy with tachycardia and may experience a marked drop in their blood pressure, resulting in collapse and loss of consciousness. Cardiovascular involvement commonly goes hand in hand with skin or respiratory manifestation^[7,57]. Death rates are very low but usually very tragic.

Anaphylaxis

This is a serious form of an IgE-mediated hypersensitivity allergic reaction involving more than one organ system, including the respiratory tract, gastrointestinal tract, and/or skin. It's rapid in onset and potentially fatal^[41]. ⁵ Even though it is rare, anaphylaxis can also present with only cardiovascular or neurological symptoms such as dizziness, weakness, tachycardia, hypotension, cardiovascular collapse, or unconsciousness^[57]. The World Allergy Organization classified anaphylaxis into five grades. The classification is made based on the number of organ systems involved, the severity of the morbidity

induced by the allergic reaction, subjective measurements such as the forced expiratory volume in 1 second (FEV1), response to treatment given. Grade 1 described mild morbidity; meanwhile, death is the outcome of grade 5^[61] (Table 1). For simplicity, acute allergic reactions that involve skin such as urticarial rash, lips swelling, eye swelling, or abdominal pain and vomiting only are usually classified as mild to moderate. However, if one or more of the above symptoms are associated with cough, hoarseness of voice, stridor, wheeze, difficulty in breathing, pallor, or collapse, the reaction will be described as anaphylaxis. Anaphylaxis is life-threatening, but in most cases, it doesn't produce a severe outcome and rarely causes death. Despite the existence of many local and international guidelines for making its diagnosis, the diagnosis of anaphylaxis remains subjective to a greater extent. Biochemical testing such as serial measurements of serum tryptase during the acute presentation and at one hour later has been introduced to help make an accurate diagnosis of anaphylaxis when in doubt.

The term biphasic reaction refers to a second Biphasic reaction that describes a second surge of histamine from degranulated mast cells after the initial symptoms of anaphylaxis settled. It's reported to occur in about 10% of patients who suffer an anaphylactic reaction. Hypotension is linked to severe morbidity and mortality when it happens, and its incidence is estimated to be 3% in the cases of anaphylaxis in children^[62].

Risk factors for severe anaphylaxis

Risk factors most strongly associated with fatal or near-fatal anaphylaxis include the type of allergenic food, adolescence or young adulthood, the presence of concomitant asthma, and the delayed use of, or lack of access to, an epinephrine autoinjector^[41,62]. Also, several factors, including exercise, viral infections, menses, emotional stress, and alcohol consumption, place some persons at increased risk by lowering the reaction threshold after exposure to an allergen.

ALLERGY HISTORY TAKING

A good history is crucial for making an accurate diagnosis of food allergy. The use of “allergy-focused clinical history” is universally recommended as it considers all the events and history related to the allergic reaction. A thorough inquiry about the personal and family history of atopy is also required. At least 30 min should be allocated to the first allergy consultation. In the case of IgE-mediated food allergy, the record is usually good enough for reaching the diagnosis. The National Institute for Health and Care Excellence produced a document on the quality standards of food allergy services in the United Kingdom, highlighting the importance of history taking in diagnosing food allergy and formulating any further management of the allergic patient^[63].

Similarly, the European Academy of Allergy and Clinical Immunology had an essential role in standardising the allergy-focused history to maximize its value as an important diagnostic tool. It also considered the patient’s age to produce age-specific standardised account-taking formats for children and adults to be used by paediatricians, physicians, family physicians, allergists, and dietitians^[64]. In 2009 the Royal College of Paediatrics and Child Health published its allergy care pathway, a reference for taking an allergy-focused clinical history in paediatrics^[65].

INVESTIGATIONS IN FOOD ALLERGY

A variety of *in vivo* and *in vitro* diagnostics have been developed to assist with diagnosing food allergy.

In vivo tests

Skin prick test: It is the most commonly used test when investigating food allergy in children and adults. Usually, it is performed during the first visit and can also be repeated later to compare the size of the wheal produced by the allergen in question. This would help predict any development of natural tolerance or decide to conduct an OFC, which would help advise on either the continuation of avoidance or instead, to allow food reintroduction.

The skin prick test (SPT) is conducted using standardized extracts from different foods and environmental allergens such as house dust mites, pollens and animal dander. A drop of the standardised allergen solution is usually put on the child's forearm or back then scratched with a lancet or a pointed device, aiming to prick the skin through the placed drop of the solution. Two drops of saline (negative control) and histamine (positive control) are used to validate the results; *i.e.*, a positive impact for normal saline or a negative effect to histamine would void the test results. While the former development could occur in individuals with dermatographism, the latter could indicate that the child has received antihistamines within 24-72 h of the test. After pricking the skin, the solution left on the skin is wiped by tissue as it may irritate the skin and sometimes makes it difficult to measure the reaction produced after 15 min. SPT uses standardised solutions produced by several manufacturers. The assessment of the wheal or erythema is used to determine the positivity of the test, with a wheal of ≥ 3 mm indicating a possible clinical allergy^[65]. Another criterion for interpretation is to compare the wheal produced by the allergen solution to the one developed by the positive control (histamine). The test is considered positive if the wheal diameter made by the antigen extract is equal to or larger than the positive control. Most importantly, the SPT result should always be interpreted in the context of the patient's clinical history. A positive skin test only identifies sensitisation to the particular allergen but does not necessarily indicate a clinical allergy.

SPT is very informative for the child and the parents. It serves as a visual aid to reinforce the need for compliance with the avoidance of particular food, and it is usually performed in the clinic. Cost is low, especially when compared to other tests such as Component resolved diagnostics (CRD), where the number of tests, and thus prices, increase significantly with the required multiple components. Urticarial rash and itching can cause discomfort. Conducting and interpreting the test can also be challenging in individuals with eczema. A systematic review and meta-analysis found that the sensitivity of SPT ranges from 68 to 100 %, with a specificity of 70 to 91 %^[66].

Recognisable wheals have been observed in 3-month-old infants, and some clinicians perform the test in infants from any age. However, the wheel size increases with age from infancy to adulthood, reflecting the change in this immune response. SPT is generally a safe procedure and is easily interpreted by trained professional staff. Emergency equipment and drugs should be readily accessible in case of any systemic adverse reactions to the allergen solution^[67].

In vitro tests

Allergen-specific IgE: The serum's measurement of specific IgE, commonly known as the RAST test through enzyme-linked immunosorbent assay (ELISA) technique, is being used nowadays instead of the old RAST. In the allergen-specific IgE (sIgE) test, the allergen extracts of the allergen of interest are chemically attached to plastic test tubes or put into multiple wells in sensitised test plates where a tiny volume of the patient's serum is added. As a result, any amount of the sIgE to the allergen will stick to the tube. A radiolabeled anti-IgE is then added and, after incubation and washing, the radioactivity is measured. The result is expressed in numbers with a standard reference. Although more expensive than SPT and, despite the length of time to yield its effects, the sIgE test is widely used. It remains an excellent alternative to SPT in patients with severe eczema or if systemic antihistamines have been taken within 1-3 d before the SPT^[68]. The Immuno solid-phase allergen chip test uses microchip technology to detect specific IgE antibodies in a tiny blood sample to 112 food and airborne allergens using the same ELISA technique. Results need to be carefully interpreted due to the possibility of cross-reactivity between food proteins.

The total serum IgE concentration has lost its importance as one of the diagnostic tools in food allergy. It is commonly raised in atopic children with eczema, parasitic infestations, and immunodeficiencies. Additionally, low levels cannot rule out the existence of IgE-mediated food allergy.

CRD: Food components testing emerged in the 1990s as a diagnostic test capable of measuring IgE antibodies to specific components contained in the allergen of interest. Contrary to the basic old concept that cow's milk and food plants each have a single protein determining its allergenicity, it became evident that every food plant has a range of heterogeneous protein components that may differ in their heat and acid stability as well as in their allergenicity.

By having specific information about the allergenicity and heat stability of a particular component to which a child is sensitised, a more specific individualized action plan can be drawn up depending on whether or not the child can tolerate, the cooked/baked form of that food (if sensitised only to a heat-labile component(s)). It can also help decide if the child or parents need to carry an adrenaline auto-injector as determined by the allergenicity of the sensitised element (s)^[69]. Sensitisation to peanut lipid transfer proteins such as peanut Ara h1 and Ara h2, both heat and proteolytic resistant, would produce severe systemic reactions. At the same time, sensitisation to the peanut Ara h8 component alone would only have oral symptoms^[69]. Some data showed that sensitisation to certain proteins is linked to prolonged allergy, as in the case of Gal d1 and Gal d2 epitopes of hen eggs^[70].

Like other allergy diagnostics, CRD should not be solely used to diagnose food allergy and should only be requested by clinicians competent in interpreting its results. More than 4700 food components have been discovered, adding complexity to the test. CRD can also help diagnose PFS and distinguish it from true IgE-mediated food allergy, where the primary sensitisation occurs to food proteins rather than pollens. The two conditions' management, severity, and outcome are very different.

Basophil activation test: SPT, sIgE, and CRD are not capable of accurately diagnosing cannot accurately diagnose food allergy because they only detect sensitisation by measuring specific IgE to whole food protein or its components. Sensitisation does not mean allergy. Cross-reactivity is common, especially in children with atopic dermatitis. Also, some non-allergenic components such as polysaccharides can trigger the

production of specific IgE of no clinical importance as it cannot produce an allergic reaction. The role of basophils is similar to mast cells in IgE-mediated food allergy, with both sharing similar high-affinity IgE receptors where specific IgE antibodies attach to their surface. As with mast cells, the basophil degranulates when re-exposed to food allergens. Detecting and measuring the degranulation of basophils by flow cytometry gives the opportunity to test for allergy rather than just sensitisation, likening the basophil activation test (BAT) to a “food challenge in a test tube”. BAT can compensate for SPT, sIgE, and CRD testing deficiency. BAT results were 92% in line with the double-blind placebo-controlled food challenge in one study. This method is becoming increasingly used, and several commercial forms are currently available. However, its use is still restricted to research laboratories and tertiary centers, and large-high-quality studies to standardise BAT are still lacking^[69]. If BAT can replace the OFC, it would be considered one of the major successes in allergy.

OFC: Blood tests or skin prick tests cannot accurately predict the severity of the allergic reaction. ¹⁵ OFC is the standard gold test for making the diagnosis of food allergy. It consists of the oral administration of incremental doses of the suspected allergen, *e.g.*, cow’s milk or peanut. It requires a physician, a nurse, space, and rescue medications. OFC is commonly performed in-office or clinic settings, especially for low-risk challenges. High-risk challenges, such as previous anaphylaxis and FPIES, should always be conducted in a safe environment with full resuscitation facilities to treat anaphylaxis.

OFC is an ideal diagnostic test used to either confirm or rule out food allergy when the history of alleged allergic reaction to food is inconsistent with the SPT or the blood tests or when the clinician or parents want to explore the option of food alternatives in children with multiple food allergies. Most importantly, it is used before food reintroduction, when the latest SPT or sIgE show that they may grow out of their allergy, which might have caused anaphylaxis in the past. The natural history of some food allergies, such as milk, is that it always occurs in the first year of life, but most children grow out of it quickly. Home reintroduction for parents who witnessed their infant suffering from

anaphylaxis is not a good option for them or the child. Thus, they may never reintroduce cow's milk even with their doctor's reassurance and even when the allergy markers suggest the development of natural tolerance to it.

Any regular antihistamines should be discontinued at least 48 h before the challenge. When performing the challenge, the doses should be increased gradually until a typical food serving appropriate for the child's age is consumed. The total weight or portion of the food can be divided into four or six parts. A negative challenge is valid if no symptoms are observed following exposure to the problematic food in an amount equivalent to a standard serving. The medical team will keep the patient for symptoms for up to several hours after the challenge. The procedure should be delayed if the child is unwell with cold, flu symptoms, or suffering from an asthma exacerbation. The latter is especially important if the child with asthma has received a short-acting beta-agonist or beta-blockers earlier. It may increase the risk of allergic reactions and antagonises the effect of anaphylaxis rescue treatment. Ideally, the child and parents would be allocated to a calm and relaxing area, preferably with a play specialist available. Usually, parents will be requested to bring the food for the challenge, but this depends on the hospital policy. The paediatric dietitian will liaise with the allergy nurse or the doctor to determine the weight and portion of the food needed for the challenge. Usually, the food is given to the child by their parents, under the observation of the medical staff. The challenge should be called off if the child develops apparent symptoms or signs of allergy such as hives, vomiting, change in behaviour, cough, stridor, pallor, or any other suggestive manifestations. The clinician responsible for the challenge should be immediately informed and treatment provided instantly^[70]. If the symptoms or signs are very subtle, not convincing, or thought to be just a skin irritation to the food rather than an allergic reaction, the same dose can be repeated. The child is observed throughout the procedure, with vital signs and examination before each incremental amount and whenever a reaction is suspected. Should the child pass the challenge, it is recommended that they continue to consume that food regularly to prevent re-sensitisation.

OFC is time and staff-intensive. A single food challenge may take up to 4 h, and occasionally the child may refuse to eat or drink the challenging food. It is acceptable to stop the procedure should the parents request it, even without a valid reason.

References are available for serum level of sIgE and the wheal size of SPT to typical food to help predict and increase the rate of successful OFC. Although these diagnostics cannot be wholly relied upon, they may encourage clinicians and reluctant parents to accept the OFC. Passing the OFC would enable parents to re-introduce certain essential foods such as milk, egg, and fish, which could have been avoided earlier. It also reduces the stress experienced by the family and helps improve their quality of life and the child's nutritional status. The success rate of passing OFC is estimated to be around sixty percent, with the most commonly encountered reactions being mild to moderate and the occurrence of anaphylaxis being infrequent^[71]. The responses should not put the clinician off from doing OFC. Anecdotally, some allergists even state that if a clinician does not see reactions while doing OFC, they may not challenge suitable patients.

TREATMENT OF FOOD ALLERGY

There is no approved medical treatment for food allergy that develops a permanent tolerance. Treatment remains primarily based on counseling the patients and their families to avoid offending food, carefully read food labels, take precautions when dining out in restaurants and parties, and be mindful of mistakes caused by a language barrier when traveling abroad. All parents of a child with a food allergy should be provided with an individualised written allergy action plan. This usually includes the name of the culprit food(s), information on how to detect an allergic reaction, when and how to use the rescue medications such as an oral antihistamine or an adrenaline auto-injector device, and what to do next. A copy should also be given to school nurses.

Oral immunotherapy

There has been a significant increase in oral food immunotherapy trials, with the majority focusing on developing oral immunotherapy (OIT) for peanut, cow's milk, and hen egg

allergy. These trials were based on the old concept that the continuous introduction of small amounts of allergenic food would induce tolerance over weeks or months. These protocols were designed to induce tolerance while ensuring children's safety^[71]. In real life, food OIT is still not widely available for all children with food allergy, and its use is minimal due to the absence of formally OIT-approved protocols in most countries. The treatment is commonly initiated at the parents' request and on their responsibility.

The first FDA-approved food allergy medication designed to treat peanut allergy, Palforzia, a peanut allergen extract, has shown success in double-blinded placebo-controlled trials, with 67.2% of Palforzia recipients tolerating 600 mg of peanut protein when challenged, compared to 4% of the placebo arm of the study. The treatment carries a risk of provoking anaphylaxis, more during the initial dose-escalation phase more than during the up-dosing and maintenance phases. A significant limitation of this treatment is that it is not a definite cure because the patient would only be able to tolerate a limited portion of peanut by the end of the treatment. However, many clinicians, parents, and patients consider it a success and a life-saving treatment. More research is required to develop a treatment that can produce long-term natural tolerance without exposing the patients to the risks of severe side effects and anaphylaxis during treatment.

OIT duration usually extends over many months or years. Some suitable treatment protocols currently under trial hope to allow the child to consume a total age-proportional volume of milk by the end of the treatment. So far, none has the formal approval of local, national, or international accredited bodies. It has also been shown that in a standard allergy clinic setting, 79% of the children with peanut allergy tolerated the desensitisation protocol and maintained it afterward by consuming a daily dose of peanut^[72]. Other studies had shown that some participants, who were successfully desensitised earlier, developed later eosinophilic oesophagitis due to regularly consuming the allergenic food at a sub-allergenic dose subsequently improved when the treatment was later aborted^[73]. Similar protocols have been created for cow's milk and hen egg allergy children. Although most participants did not experience significant reactions, a small number developed anaphylaxis during the treatment. It remains

unclear if OIT would eventually produce tolerance similar to when these children naturally grow out of their allergy, or if it only induces transient desensitization. Some treated patients lose the patience once they stop taking the maintenance amount of the offending/ allergenic food. Thus, some consider this kind of treatment an additional risk rather than a therapy^[74]. More work is required to provide safe and efficient protocols that can be applied to everyday practice by addressing the encountered short and long-term complications of the OIT. Moreover, different routes such as epicutaneous or sublingual are currently under study.

Adjuvants

Adjuvants are frequently added to vaccines to boost their immune response and reduce some undesirable reactions. Its role has been investigated in OIT for improving its response in terms of the longevity of its effect and the reduction of side effects. Aluminum salt is one of the most popular vaccine adjuvants used. Still, its use as an adjuvant in the treatment of peanut allergy was disappointing due to the side effects encountered, especially when tried along with subcutaneous peanut therapy^[75].

Probiotics

Studies have confirmed the role of intestinal microbiota in supporting the early establishment of immune tolerance and reducing the risk of developing allergic disease early in life. In the first few days of life, the newborn baby's gut becomes inoculated by bifidobacteria, lactobacilli, and other non-aerobic bacteria. Other bacteria such as streptococci, staphylococci, lactobacilli, and bifidobacteria in breastfed infants also colonise their gut. Interacting with the host gut, these bacteria play a beneficiary role in the absorption of nutrients, interfere with the growth of pathogenic organisms, and are also essential for developing immune tolerance to different antigens, including food antigens^[76,77]. Most studies on the function of probiotics in food allergy management have focused on their role in managing cow's milk allergy. A systematic review of nine trials involving 985 patients with cow's milk protein allergy has demonstrated moderately

encouraging results with probiotics, showing that the use of *Lactobacillus rhamnosus* GG can help infants with suspected cow's milk protein allergy to develop tolerance^[76,77].

Biologicals

Omalizumab is one of the most common biologicals investigated to enforce and speed up tolerance during oral food immunotherapy. In a double-blind placebo-controlled trial comparing it as a catalyst in the treatment of cow's protein milk allergy to a placebo in 57 participants aged between 7 to 32 years; no difference was found in the number of participants desensitised to the cow's milk protein in the two arms of the study. However, there was a marked reduction in the allergic reaction that needed resuscitation with adrenaline in the omalizumab arm^[77].

Studies of omalizumab have been performed to improve the safety of OIT and find out if it could speed up a tolerance to cow's milk and peanut in food allergic individuals. In the cow's milk study, 92% of the participants could reach the maintenance dose, although almost half suffered moderate to severe reactions during the induction phase. In the peanut study, 88% of the participants tolerated the induction phase, with only 2% continuing to encounter allergic reactions, with some requiring adrenaline to treat anaphylaxis^[78,79].

From the available evidence, omalizumab offers some benefits as a mono booster for desensitization in food allergy, but its benefit remains limited. More work is required to support biologicals either as monotherapy or other adjuvants in desensitizing food allergy.

The role of baked food

There are strong hypotheses that introducing baked food, such as biscuits or cake containing milk or egg, respectively, in children with cow's milk and egg allergy, would expedite the development of natural tolerance to these foods of high nutritional value. The baked form of the food is usually less allergenic than the raw or lightly cooked form, as cooking at high temperature alters the conformational epitope of the food proteins,

making them less allergenic to the sensitised child^[80]. It has been estimated that almost two-thirds of children with cow's milk allergy can tolerate the baked milk in biscuits and the egg in cakes and that the continued ingestion of the baked form of these foods speeds up the induction of natural tolerance. This observation has been noticed with both IgE-mediated and non-IgE-mediated allergies. Some researchers are unconvinced of baking the food in inducing natural tolerance of the allergens. One reason is the short and limited natural self-limiting history of cow's milk and egg allergy, and the other is that those children who tolerate the baked form of milk and egg may have an allergy phenotype that enables them to take the baked forms of the food, and thus rapidly grow out of the allergy^[81]. However, the benefit of introducing baked milk or egg remains a success story, not only because of the added nutritional value of these foods to the allergic child but also in helping to reduce parental stress and anxiety. Another benefit to those children is decreasing their risk of developing food aversion to milk and eggs.

The role of the early dietary introduction of potentially allergenic food and food allergy prevention

Until now, infant and young children's feeding and nutrition international advisory boards, such as the World Health Organization and United Nations International Children's Emergency Fund, advise parents and professionals dealing with children to delay the introduction of the common allergenic foods such as peanut, egg and cow's milk to breastfed babies. This consensus recommendation was made due to the remarkable rise in food allergy prevalence among children. To promote natural breastfeeding, the introduction of cow's milk was also discouraged in breastfed babies in the first 6 to 12 mo of life.

Unfortunately, over the last few decades, what was observed depicts an opposite effect, as the prevalence of food allergy in children continued to rise despite that conservative approach. This led the international food and allergy community to revise the current recommendations and also prompted researchers to conduct multicentre clinical trials to compare the effect of the early introduction of allergenic food with the current

8
recommendations. Learning Early About Peanut Allergy (LEAP), a study published in 2015, gave concrete evidence that early introduction of peanuts can significantly prevent the development of peanut allergy in many infants and very young children^[82]. The LEAP study was a game-changer that overshadowed all the previous international guidelines and recommendations. More studies followed, investigating the early introduction of egg and cow's milk and resulted in similar outcomes. The introduction of the egg at the age of 4-6 mo helped reduce the development of egg allergy compared to those who had egg introduced at 10-12 mo^[83]. Some countries, such as Canada, took the lead and started to change their infants' feeding recommendations with the early introduction of peanut butter for children with mild to moderate eczema at 6 mo. For infants with severe eczema or severe egg allergy (<1%), the introduction needs to be done under medical supervision with a skin prick test initially followed by a home or hospital-graded introduction. In case of high sensitisation, the introduction should be avoided if the skin prick test results in ≥ 8 mm wheal^[84].

We hope to see significant changes in the coming years on the recommended age of weaning infants into semisolids and the early introduction of certain foods previously avoided below the age of 6 and 12 mo. The real challenge would be to come up with a set of comprehensive and clear guidelines to advise on the recommended age of introduction of the different allergenic foods and the amount and the frequency of meals to be given. Alternatively, the new guidelines could be more pragmatic and leave it to parents and the baby's tolerance to dictate when and how to introduce these foods.

Food allergy and parental anxiety

Food allergy in infants and young children causes significant stress and puts a heavy burden on parents' shoulders. The psychological effects vary from anxiety and stress to depression. These manifestations were observed more often in mothers, peaking at certain stages in their children's lives, such as when they join nursery or school. While in other medical conditions, control is achievable by using medications and avoiding

specific obvious triggers, with food allergy, the accidental exposure to a hidden ingredient could happen “anytime and anywhere”, as described by one parent.

The allergenic food could be a component of a benign food fed to the child unknowingly, ingested due to poor labeling or simply because another child at school shared his food with the atopic child. The stress is amplified if parents had already witnessed their child having an anaphylactic reaction, where they feared for their child. Such pressure could affect the parents’ entire life and undermine their sound ability to make the right decision in their daily life. It may also negatively impact how they look after their allergic child and provide treatment during anaphylaxis.

It is important to spend part of the allergy consultation listening to the parents’ fears and invite them to talk about what they feel and the worries they have about their child’s allergic condition. Many studies have addressed this issue by evaluating the stress produced, quality of life, and how normal activities (school, work, dining out, attending events, travel, and normal social life) have been affected. Some studies have recommended mandatory referral of the parent to the local psychological service for support and counseling, as their stress may affect their quality of life and the way they respond to their child’s medical needs. Psychological support and cognitive therapy would support these parents in finding a balance between keeping their child safe, living, and enjoying a nearly everyday life^[85].

Natural history and prognosis of food allergy

Most children with cow’s milk and egg allergy do grow out of sometimes even before school age^[86]. However, tree nuts, peanut, fish, and shellfish allergy are commonly persisted. Peanut is widely known for the aggressiveness of its allergic reaction. However, data in recent years have shown that severe morbidity and mortality have been linked to cow’s milk and sesame allergy. Children with sesame allergy are growing worldwide for no apparent reason^[43]. In addition to cow’s milk, egg, seafood, peanut, and tree nuts, wheat, soy, and legumes are allergic foods. Tolerance induction is expected when the level of specific IgE antibody to the particular food significantly drop during

six or twelve monthly monitoring, usually followed by home or hospital supervised reintroduction^[6]. Interestingly, sometimes tolerance is diagnosed with the child accidentally ingesting the offending food, but to the parent's surprise, doesn't develop any signs or symptoms.

CONCLUSION

There is a pressing need to develop new allergy tests that can accurately diagnose and predict the severity of any potential reaction. Future research is also needed to create simple and quick diagnostic tests to inform clinicians and parents when the child may grow out of food allergy.

There is no approved definite treatment that can produce lifelong natural tolerance. Adrenaline autoinjector (AAI) remains the drug of choice in treating anaphylaxis. However, studies showed that parents underuse it due to a lack of empowerment or knowledge with its indication or simply because they do not know how to use it. Data also showed a worrying attitude by teenagers towards the use of AAI mainly related to risk-taking behavior commonly seen in this age group. Further studies are still needed to elucidate other reasons for underusing the AAI. Better training with audio-visual aides, alongside psychological support for the patients and parents to find a balanced lifestyle, is still required. Adrenaline autoinjectors need to be made available in public places such as malls, bus stations, and schools, as the child's first-ever noticeable food allergy reaction could be a severe and life-threatening one.

More research into feeding recommendations with early introduction of allergenic food such as peanut, egg, and cow's milk is also needed.

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