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Food Allergy Overview in Children

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Abstract Food allergies have increased significantly in the past decade. An accurate history is crucial in approaching the management. At the outset, food intolerance must be distinguished from food allergies and, furthermore, these allergies should be classified into either an IgE, Non-IgE, or a mixed response. The clinical features vary from life-threatening anaphylaxis to milder IgE-mediated responses, atopic dermatitis, and gastrointestinal symptoms. The severity of the reaction and the potential risk for anaphylaxis on reexposure should be assessed. Milk, soy, egg, wheat, and peanut allergies are common in children, whereas peanut, tree nut, fish, shell fish allergies, and allergies to fruits and vegetables are common in adults. Structural proteins are important determinants of the severity of the reactions and may often predict the natural history and cross reactivity. Diagnostic work up must be guided by the clinical history. Skin testing and food-specific IgE done by standard methods are very useful, whereas oral challenges may be indicated in some situations. Majority of the patients outgrow their allergies to milk, soy, egg, and wheat, and some to peanut also, therefore, patients should be periodically reassessed. Novel diagnostic techniques which detect specific allergenic epitopes have been developed. Several newer therapies are promising.

Keywords Food allergy · IgE-mediated reactions · Non IgE mediated reactions · Food allergens · Plant structural proteins · Cross reactivity · Cross contamination · Peanut allergy · Tree nut allergy · Milk allergy · Soy allergy · Cereal grain allergy · Fish allergy · Crustacean allergy · Fruit and vegetable allergy · Lentil allergy · Dyes and preservatives · Food additives · Diagnosis · Newer diagnostic methods · RAST tests · Skin tests · Oral challenges · Management · Natural history · Prevention

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Food Allergies

Adverse food reactions consist of a variety of abnormal reactions to food or food additive ingestion. The majority of these responses is not allergic in nature and is caused by food intolerance, which are the effects of the pharmacologic property of the food. Examples include caffeine-causing irritable bowels and tyramine-induced nausea and headache. Metabolic disorders like lactose intolerance as a result of lactase deficiency or toxins in food caused by contaminants, such as bacterial food poisoning or histamine released from stale fish (scombroid poisoning), also cause food intolerance. Toxic reactions can be elicited by almost anyone who ingests a sufficient quantity of such tainted food. The clinical diagnosis of food allergy is a challenge as many children also have food aversions and feeding problems. In addition, parents have their own perceptions about the suitability and different effects of food.

Allergic or immunologic reactions are further classified into IgE-mediated and non-IgE-mediated reactions. IgE-mediated reactions are typically rapid in onset, examples are anaphylaxis and urticaria. Non-IgE-mediated reactions are slower in onset and are primarily gastrointestinal reactions. Atopic dermatitis if caused by food allergy may either be an IgE-mediated, T cell-mediated, or mixed response.

Epidemiology

Although 25% of adults perceive that they have food allergies, the prevalence of IgE-mediated disease confirmed by double-blind placebo-controlled challenges is much lower and varies between 2% and 5%. Children <3 years of age have been reported to have a higher overall prevalence rate of 6% [1]. More recently, a prospective birth cohort study looking at the incidence of parental reports versus clinically diagnosed food hypersensitivity in the first year of life has demonstrated a prevalence of 3.2–4% as confirmed by challenges, whereas the cumulative incidence of parental perception of food allergies in their infants was as high as 25% in this study [2]. Determination of the exact prevalence of food allergies is complicated by the fact that there is considerable methodological variation in data collection. Reports are based on either self-reported questionnaires only, physician assessment, skin tests, and/or IgE levels are included in some, and a few are confirmed by double-blind placebo-controlled challenges. Many of the reports do not distinguish between IgE- and non-IgE-mediated responses, some even include nonspecific contact reactions. Other important issues include the fact that most reports look at only one or a few of the common allergens, besides, the ages of the patients vary in the different studies. Different geographic locations, diet, ethnicity, and whether or not these patients are drawn from an unselected population or a tertiary allergy referral center are also contributing variables. In general, food allergy manifests most commonly in infancy, peaking at 1 year of age and declining by age 3. Milk, egg, soy, wheat, peanut, and tree nuts account for over 80% of the reactions in children whereas in adults, peanuts, tree nuts, shellfish, and fish are common. Allergies to fresh fruits and vegetables, the most common reactions reported by adults, are more prevalent in Europe even in children, but are generally not severe. An unselected population of a thousand children and a thousand adults was studied in Denmark and the prevalence of possible food allergies was recorded to be 16.6%; reactions as confirmed by oral challenges were 2.3% in children 3 years of age, 1% in children older than 3, and 3.25 in adults [3]. The most common reactions were to eggs affecting 1.6% of children aged 3 and peanuts affecting 0.4% of the adults. Adults reacted to shrimp 0.3% and codfish 0.2% whereas none of the children had a positive challenge to shrimp or cod fish. The prevalence of reactions to pollen-related foods in pollen-sensitive adults was estimated to be 32%. Worldwide, there is a significant increase in food allergies in the past decade. Reactions to exotic culinary ingredients as well as allergies to foods specifically consumed by different ethnic groups are increasingly reported in the literature.

Pathogenesis

The GI tract is exposed to an enormous load of potential allergens including bacteria, viruses, and food. Despite these exposures, food allergies are relatively uncommon. The GI tract has several mechanical barriers to prevent the absorption of foreign antigens. Gastric acid digests the proteins, rendering them less antigenic [4]. Other factors like secretary IgA in the GI tract, binds foreign protein, whereas mucous secretion and peristalsis helps the gut to clear its antigenic load. Decreased proteolytic enzymes, low IgA levels, relatively low PH, and an immature gut barrier makes infants vulnerable to develop food allergies. The gut epithelium has tight junctions between the cells, which prevents the passage of large antigenic proteins. Less than 2% of the dietary proteins are absorbed in an immunologically intact form. When intact proteins do cross the gut barrier, immunological defenses induce oral tolerance. Central to the induction of tolerance is thought to be the regulatory T cells, dendritic cells, and local immune responses. Several types of regulatory T cells have been identified as major players in intestinal immunity, Tr1 cells are CD4+ cells, which secrete IL-10, and TH3 cells are CD4+ cells, which secrete TGF-β. Other cells such as CD4+ CD25+ regulatory T cells, γδ T cells, and CD8+ suppressor cells also suppress allergic responses [5]. Dendritic cells play a role both in sampling of antigens from the gut and the induction of tolerance. Dendritic cells residing in the mesenteric lymph nodes stimulate CD4+ T cells to secrete TGF-β on antigenic stimulation, which in turn induces the production of IL-10 and TGF-β [6]. TGF-β plays a role in class switching to IgA.

Intestinal epithelial cells uptake luminal antigens and present them to T cells via the MHC II complex [7]. Food antigens processed through the intestinal epithelial cells induce tolerance because epithelial cells lack the critical second signal [8]. Commensal organisms in the GI tract play an important role in driving the immune responses. Mouse models have demonstrated that Toll-like receptor 4 signals provided by the intestinal bacteria inhibit the development of allergic responses to food antigens [9]. There appears to be a critical window in the neonatal period when these allergic responses are induced.

The development of allergies to food proteins also depend on the structure of the protein, dose of the antigen, and the genetic susceptibility of the host. Genetic risk factors include a family history of atopic diseases. Although no specific gene has been isolated, a twin study showed a concordance rate of 64% in identical twins compared to only 7% in fraternal twins in the development of peanut allergies [10]. The association of HLA class II genes have been shown in a case control study [11]. Food allergy appears to be the first manifestation of the "atopic march" with a significant number of infants

with atopic dermatitis progressing to develop allergic rhinitis and asthma.

Food Allergens

Sensitization to food can occur either primarily through the GI tract (class I allergens) or secondarily through the respiratory tract via inhalation (class II allergens) [12]. The majority of the class I food allergens are heat stable, resistant to acid degradation, and resistant to proteolysis. Class I allergy is seen mainly in children and is rare in adults. Important allergens include cow's milk proteins (casein, whey), egg (ovalbumin, ovomucoid), peanut (vicillin, conglutin, glycinin), shellfish (tropomysin), and fish (parvalbumin). Extraintestinal sensitization may also occur. This has been demonstrated not only in mice models that showed epicutaneous sensitization to egg protein [13] but was also observed in an epidemiological study showing increased peanut allergy amongst children in UK who were found to have been sensitized to peanut protein via topical application of an emollient [14]. Sensitization to the class II allergens, which is mainly seen in adults, occurs initially to inhaled plant and tree pollens. IgE-mediated reactions may subsequently occur when foods containing cross-reacting epitopes are eaten as seen in the oral allergy syndrome. Class II allergens are usually labile proteins, which are easily degradable.

Plant food allergens are classified based on their structural and biological properties into families and superfamilies [15]. Majority of them belongs to the cupin (7S and 11S seed storage proteins) or the prolamine superfamilies (2S albumins, nonspecific lipid transfer proteins (nsLTP), α-amylase/trypsin inhibitors) and the prolamine storage proteins of cereals [15]. Seed storage proteins are responsible for many of the systemic reactions. Examples include peanuts and tree nuts in addition to reactions to mustard and sesame. Plant allergens have also been found in pathogenesis-resistant proteins (PRs); these proteins help plants defend against plant pathogens. PRs cause the pollen–fruit or latex–fruit syndromes. Food allergens are also seen in the profilin family.

Structurally, the immunogenic proteins are formed by either conformational or sequential epitopes. Conformational epitopes, formed by the tertiary structure of the protein are degraded by heating or enzymatic action, whereas sequential epitopes are relatively resistant to processing and are thought to be responsible for the more severe and lifelong allergic responses.

Clinical Features

Food allergies cause a wide spectrum of clinical features depending on the nature of the reaction. Acute, IgE-mediated reactions commonly present with urticaria and pruritis more severe reactions causing anaphylaxis. These reactions typically occur a few minutes to within an hour of consuming the food. If the reaction occurs a few days after consuming the food, it is not likely to be IgE-mediated. Although food allergy accounts for 20% of acute urticaria, chronic urticaria is unlikely to be caused by food allergy. Food allergies could also present with GI symptoms or atopic dermatitis. Isolated respiratory reactions are very rare. Contact dermatitis is seen among food handlers, particularly in those handling raw fish, shellfish, eggs, and meat.

Peanut Allergy and Tree Nut Allergies

Peanut allergy is often associated with life-threatening anaphylaxis and is the leading cause of fatal food-induced anaphylaxis [16, 17]. Allergies to peanuts present with reactions limited to the skin manifested by urticaria or atopic dermatitis in a large number of patients. Peanut allergy has significantly increased globally in the past decade as shown by several epidemiological studies. Peanut sensitization increased threefold from 1989 to 1996 in an unselected study [18], which looked at two sequential cohorts 6 years apart in the Isle of Wright (UK) involving over a thousand children; the estimated prevalence of peanut allergy was 1.5%. In this study, most of the skin prick tests were also confirmed by oral peanut challenges (unless there was a history of a systemic response). The point prevalence of peanut allergy confirmed by oral challenge in a recent cohort of unselected Danish adolescents was estimated at 0.5% [19]. The prevalence of self-reported allergy to peanuts and using a random-digit dial telephone questionnaire-based survey of almost 5,000 households in the United States reported the prevalence of peanut allergy, tree nut allergy, or both to be 1.04%. In children, the prevalence rate of peanut allergy had increased from 0.6 in their previous survey in 1997 to 1.2% in 2002 [20].

The reason for the increase in prevalence is perhaps caused by the increase in peanut consumption. In UK, an association of topical application of emollients containing arachis oil was shown to be associated with the increased prevalence of peanut allergy in young children. Different processing methods have a bearing in the development of peanut allergies [21]. Dry roasting at high temperatures increases the allergenicity of peanut protein in contrast to boiling or frying [22, 23]. Although the amount of peanut consumption in China and the USA are comparable, peanut allergy is uncommon in China as boiled or fried peanuts are eaten, rather than dry roasted peanuts, which are commonly consumed in the US. Increased soy consumption has also

been postulated to be responsible for the increase in peanut allergies.

Several major and minor peanut allergens have been determined, and the major allergens are Ara h 1, 2, and 3 [24]. Proteolytic digestion of native Ara h 2 produced stable fragments, which were resistant to subsequent digestion; these fragments contained intact IgE-binding epitopes. In addition, the structural nature of the fragments protected these sequences and the sites prone to enzyme digestion [25]. Ara h 1 consists of two isoforms, one of which binds to a greater number of epitopes [26]. The degree of clinical reactivity to peanut, the range of clinical manifestations, and cross reactivity may be explained by the fact that individuals selectively react to the different allergenic epitopes and/or cross react with several epitopes of significance.

Although peanuts and tree nuts belong to different botanical families, peanut-allergic patients reportedly have a significantly high degree of co-reactivity to tree nuts. Clinically, the degree of co-reactivity to tree nuts in peanut-allergic patients has been reported to be as high as 23–50% [27]. These numbers are obtained from studies looking at selected patients referred to specialists, which probably represents a population that has multiple allergies with exquisite systemic sensitivity. In comparison, a prevalence rate of 2.5% in the random-digit dial tree nut and peanut questionnaire surveys in an unselected population in the US was reported. On a structural level, homologous proteins between peanuts and cashew nut, as well as peanut and hazelnut have been demonstrated [28]. Co-reactivity has also been reported between peanut and seeds like sesame, mustard, and poppy, and the peanut proteins Ara h 2, 6, and 7 has been shown to share sequence homology with seed storage proteins [15].

Clinical cross reactivity between peanut and soy, which is also a legume, is extremely rare despite the high degree of cross-sensitization based on IgE-binding and skin tests [27, 29]. Similarly, peanut-allergic patients do not usually react to other legumes such as green beans, navy, and lima beans; and reactions to peas in peanut-allergic children are also rare. Exceptions to this rule are certain ethnic populations, geographic locations, and perhaps exposure to more sensitizing legumes such as chickpeas and lentils. As a general rule, 95% of the peanut-allergic patients can tolerate soy and other legumes [27].

Peanut allergies were thought to persist for life. Observations in the UK in a case controlled study showed that 9.8% of the patients lost their peanut sensitivity [30]. Confirming this observation, in a subsequent study, peanut-allergic patients who had not reacted in the past, with a peanut-specific IgE <20 kU_A/l were challenged, and 21.5% tolerated the challenge [31]. In this report, a significant proportion of the peanut-allergic children had other concomitant food allergies with 55% having positive challenges to egg, 41% to milk, 15% to soy, and 4% to other legumes. The patients who had other food allergies seemed to take a longer time to outgrow them. Patients with atopic dermatitis appeared to have persistence of peanut allergy whereas those with concomitant tree nut allergy were less likely to outgrow their peanut allergy. Those who outgrew their peanut allergy in this report were more likely to have had the initial reactions limited to the skin only in comparison to patients who had more than three systems involved. Peanut-specific IgE levels were lower in the patients who passed the challenge in comparison to those who did not (median level 0.69 vs 2.06). Patients with IgE levels >20 kU_A/l are more likely to have positive challenges. Similar rates of asthma and allergic rhinitis were seen in those who passed or failed the challenge contrary to the UK study [30] where persistence of peanut allergy was more likely in patients with asthma and rhinitis. Based on these observations, it is recommended that patients with peanut allergy should have their IgE levels checked every year (till age 5), even those with levels >10 kU_A/l, as the occasional patient with initial high levels may outgrow their allergies. Certainly patients with levels <2 kU_A/l and those asymptomatic patients with levels <5 kU_A/l should be considered for a challenge in hospital settings under careful observation to rule out clinical sensitivity.

Skin prick test response of a wheal >8mm and a peanut- or tree nut-specific IgE level >15kU_A/l had predictive values of 95% and 92%, respectively, for a positive challenge with peanuts and tree nuts [32]. Patients were drawn both from a tertiary allergy clinic as well as a unselected birth cohort and the age, referral pattern, and the type of nut did not have any bearing on the results and oral challenges were therefore deemed unnecessary in this situation.

Children with atopic dermatitis when tested for peanuts are often found to have positive skin tests for peanut, yet many of them are peanut naïve. This situation is commonly seen in clinical practice putting clinicians in a quandary as to what to advice parents on the issues of dietary restrictions, avoidance measures, and prognosis in such cases. A similar situation arises when parents with a highly peanut-allergic child want testing for the sibling or they want a child with severe milk or egg allergy tested for peanuts also. A study looking at atopic peanut naïve children found that 49% of them developed symptoms on oral peanut challenge [33]. Sensitization to peanuts occurs at an early age, therefore, such patients are more likely to react at the first exposure to peanuts. Many children who have milk and egg allergies are potential candidates for subsequently developing allergies to other highly sensitizing food such as peanuts during childhood. Therefore, one can assume that children with such clinical scenarios are prone to developing peanut allergies. They should be

carefully evaluated before making casual declarations of peanut allergy or recommendations for peanut avoidance and accessibility to injectable epinephrine based on skin tests, which may be borderline. Peanut-specific IgE levels and quantification of skin test responses as detailed above would be very useful in such situations.

Because of the severity of the reactions associated with peanuts, there is a perception amongst many people that peanut allergies are always potentially fatal, hence considerable anxiety and emotional trauma is experienced, along with lifestyle changes, which may not be always be necessary. Therefore, it is essential to educate them to differentiate between the association of atopic dermatitis as the sole manifestation of peanut allergy and milder cutaneous reactions from the systemic responses and tailor the management accordingly. Questions often arise regarding whether or not it is safe to send a peanut-allergic child to preschool or kindergarten or the extent of exposure to peanuts that they can tolerate outside the home. Exquisitely, peanut-allergic children (median peanut-specific IgE levels >50 kU_A/l) were exposed to direct contact with peanut butter and also inhalation. Other than pruritis, local erythema, or wheal and flare reactions in some, none of them experienced systemic reactions [34]. In situations such as in ballparks or airlines serving peanuts (due to recycling of air within the confined space) or exposure to aerosolized peanut flour, sufficient concentrations of peanut protein may be air borne and cause reactions.

Other routes of exposure such as kissing and coitus has raised concerns in highly sensitive individuals as severe and even fatal consequences have occurred as a result of exposures via these routes. Salivary levels of Ara h 1 were assessed in peanut-allergic individuals after various interventions such as brushing the teeth, having a peanut free meal, chewing gum, etc. Ara h1 level was below threshold levels after 1 h and with any of the interventions [35].

Another clinical issue is the safety of peanut oil in highly peanut-allergic individuals. Peanut oil was thought to be safe in peanut-sensitive patients based on one study in which highly peanut-sensitive patients tolerated a double-blind placebo-controlled challenge with peanut oil from a single manufacturer. A study looking at peanut and tree nut oils has shown that the protein content depends on the extent of processing and varies considerably between different brands [36]. Furthermore, they demonstrated that the least processed oils had extensive peanut- and tree nut-specific IgE-binding, whereas some of the highly processed oils had no detectable protein. Cold pressed or expeller extraction is merely a mechanical process and the temperatures reached are only around 65°C to 95°C. Unrefined and many gourmet oils are expelled in this manner as the flavour and health benefits of the oil are thought to be better preserved. Chemically extracted oils undergo several steps, which may include degumming (a process of separating oil from water by centrifugation), alkali extraction, filtration and "deodorization" with steam under vacuum, and finally winterizing. These processes subjected the oils to a range of temperatures ranging from 260°C to 70°C. It is generally advisable for a peanut-allergic patient to avoid all peanut oils as the exact protein content varies by the extraction method and between different manufacturers (particularly imported and gourmet varieties); besides, there may be significant cross contamination if other highly allergic foods such as tree nuts or sesame is processed using the same manufacturing equipment. Significant amounts of peanut protein can also be present in the residual oil if peanuts are fried in any oil. The same logic holds true for tree nut oils as well.

Tree Nuts

Allergic reactions to tree nuts are very severe and has accounted for a significant number of fatalities [37, 16, 17]. The prevalence of tree nut allergies is 0.5% in the US in the unselected population survey on tree nuts and peanuts referred to in the previous section [20]. Reactions often occurred at the first exposure and two thirds of the patients experienced greater than five reactions. Almost half the patients complained of reactions to more than one tree nut. Allergic reactions to walnut, cashew nut, almond, pecan, Brazil nut, hazelnut, macadamia nut, pistachio, and pine nut were reported. Another study in which tree nut allergies were confirmed by DBPC showed that cashew nut, walnut, and pecan were responsible for the majority of the reactions and also for the more severe reactions in a selected population referred to a tertiary care allergy center, whereas almond, cashew, and walnut accounted for three quarters of the milder reactions [37]. The prevalence rate of tree nut allergy is similar in the UK [38] and hazelnut allergy is common in Europe [39]. The molecular sequences of several tree nuts have been identified and there is considerable cross reactivity between tree nuts. In general, most of the severe reactions are thought to be because of the family of seed storage proteins similar to peanut and other seeds notably sesame. Sera from all the hazelnut-allergic patients (documented by DBPC), in one study, reacted to Cor a 1, the major allergenic protein, which is homologous to Bet v 1 of the birch family allergen [40], whereas patients with severe reactions to hazelnut showed an IgE reaction to Cor a 8, a hazelnut lipid transfer protein, which is also a major allergen in Spanish patients with hazelnut allergy (without birch pollen allergy) in another study [41]. These studies once again highlight the importance of the role of structural proteins in determining allergic responses.

Tree nut allergies were thought to be lifelong, however, a study done in a tertiary allergy referral center showed that 9% of patients including those who had previous severe reactions outgrew their allergies [37]. Tree nut-allergic patients should therefore be periodically reevaluated for tolerance, and it has been suggested that patients with a tree nut-specific IgE level below 5 kU_A/l should be considered for a challenge. As discussed above, levels >15 kU_A/l and a skin test response of >8 mm are predictive of a positive challenge. Because of the high degree of cross reactivity between different tree nuts, it is better for a tree nut-allergic patient to avoid all nuts.

Pine nuts, which are tree nuts, have not been associated with severe allergies. Cocoa bean, which is also a tree nut, gets extensively processed, thereby denaturing the allergenic protein [42]; hence, cocoa allergy is extremely rare. Other ingredients in the chocolate may cause allergy to chocolate. Coconut belongs to the palm family.

Milk

Cow's milk allergy is very common in infants and young children with a prevalence rate of around 2.5% [43–45]. IgE-mediated reactions usually present with immediate responses like urticaria and angioedema but severe anaphylaxis can also occur and fatalities have been reported [46]. Some of these reactions can occur with the ingestion of very small amounts of milk or with contact alone. Milk allergy can present with non-IgE-mediated reactions such as atopic dermatitis or eosinophilic GI disorders. About 50% of patients who are allergic to milk often develop allergies to other foods, and about 80% to aeroallergens [45].

Casein the major allergenic milk protein consisting of the 1α, 2α, β, and κ fractions, whey protein which makes up the remaining 20%, comprises of α-lactalbumin and β-lactoglobulin [47]. Some patients who are milk-allergic may tolerate small quantities of milk in products such as baked goods. Tolerance to milk develops by the age of 3 or 5 years in approximately 85% of the children [43, 1]. Identification of the specific IgE-binding epitopes for casein and whey allergens explains these clinical phenomena and can also predict the likelihood of tolerance or persistence in individual patients [48].

Contrary to popular belief, patients who are allergic to cow's milk also react to goat's milk. The cross reactivity between cow's milk and goat or sheep's milk is 90% [49]; however, the cross reactivity between cow's milk and mare's milk is only 4% [50]. Around 85% of children with cow's milk allergy are able to tolerate soy-based formula; however, there is some evidence [51], which suggests that soy-based formula may be as allergenic as cow's milk-based formula. The soy protein component that cross-reacts with casein has been recently identified as the A5B3 glycinin molecule [52].

The American Academy of Pediatrics does not recommend soy as a substitute in the first year of life in a presumable effort to prevent the subsequent development of allergies to other foods in infants at risk of developing food allergies [53]. Almost all (around 98%) [51] of the infants with IgE-mediated reactions to cow's milk are able to tolerate extensively hydrolyzed milk-based formulas, which are perhaps the appropriate alternative choice. The cross reactivity between cow's milk and beef is reported to be around 13–20% [54], although the clinical reactivity is not that high and depends on the extent of alteration of the antigenic protein by various cooking methods and processing.

Egg

Egg allergy is also very common in childhood with a prevalence rate of 2.5% [1]. A population-based prospective study reported the point prevalence of egg allergy to be 1.6% as confirmed by oral challenges [55]. Almost all the reactions were IgE-mediated and tolerance to egg is usually developed by 5 years of age. Like milk allergy, reactions to egg may vary from contact urticaria, atopic dermatitis, and mild urticaria to severe systemic responses with one death because of anaphylaxis [17]. Children who are egg-allergic during infancy are at increased risk of becoming subsequently sensitized to aeroallergens [56]. Eggs are widely used in almost all baked goods. Most of the deserts, ice creams, pancakes, and French toast have considerable amounts of eggs. Eggs are often the "hidden ingredient" in creamy salad dressings, pasta, whipped cream, icing, batters, and several other preparations. Many patients with egg allergies are often able to eat baked goods. This phenomena and the development of tolerance can be explained by the nature of the individual's antigenic response to specific egg allergens. Major egg allergens are ovomucoid (Gal d 1), ovalbumen (Gal d 2), ovotransferin (Gal d 3), and lysozyme (Gal d 4). Ovomucoid is the main allergen, which is fairly resistant to cooking and digestion in comparison to Gal d 2, Gal d 3, and Gal d 4. Children with higher concentrations of IgE antibodies directed against ovomucoid were less likely to outgrow their egg allergy [57], besides, specific levels of anti ovomucoid antibodies could also predict whether or not children could tolerate heat-treated eggs such as in baked goods [58]. In addition, levels of IgE antibodies against pepsin-digested ovomucoid were useful in distinguishing challenge positive from challenge negative individuals measuring toler-

ance [59] and could also predict whether or not children with contact urticaria to egg are likely to manifest systemic symptoms on ingestion [60].

Soy

Soy allergy is fairly common in infants and children but is usually transient. The prevalence rate is estimated at around 0.3% to 0.4% [1]. Manifestations range from immediate reactions like urticaria to non-IgE responses such as atopic dermatitis and GI symptoms as a result of soy protein intolerance. Reactions are usually mild, however, isolated cases of death have been reported because of soy allergy. Soy protein is increasingly being consumed as a health food. Most vegetable oils are derived from soy. Soy lecithin is used almost ubiquitously in the food industry. Soy oil [61] and soy lecithin can be safely ingested by patients with soy allergy.

Cereal Grain Allergies

Acute IgE-mediated responses to wheat are common in children. Responses also include the unusual wheat-induced, exercise-mediated acute allergic response, which is rarely outgrown, and cell-mediated reactions such as atopic dermatitis, GI manifestation, and celiac disease. Inhalational sensitization to wheat allergen may result in occupational asthma as seen in bakers. Different allergic proteins, which are associated with the varied clinical responses, have been identified. Although cross reactivity as high as 20% has been reported between the cereal grains [62], wheat-allergic patients can usually tolerate other grains, and these cross reactions do not generally appear to be clinically important. Most children with IgE-mediated reactions to wheat usually outgrow them [1]. Rice allergies are increasingly being seen in the pediatric population with presenting with mild urticaria or atopic dermatitis. Sometimes, delayed GI symptoms with profound vomiting followed by dehydration are seen. Oat and barley allergies are seen in infants and reactions are typically mild.

Fish and Seafood Allergy

Allergic reactions to finned fish are very common particularly in adults and are associated with severe reactions and fatalities. The prevalence of sea food allergy was estimated at 2.3% [63] by a nationwide, random cross sectional telephone survey via questionnaire of over 5,000 households in the United States. Seafood allergy was more common in adults than in children and in women than men. Half of this population reported severe symptoms (dyspnea and throat tightening) and almost 60% reported recurrent reactions. Sixty seven percent reported reactions to multiple fish, whereas 38% reported reactions to more than one crustacean and 48% reacted to more than one mollusk. In this survey, only 14% with crustacean allergy reported reactions to mollusks. Double-blind placebo-controlled challenges done in patients with a history of reacting to fish have been positive in 75% with many patients having reacted to more than one species. Itching of the mouth was the most common symptom reported, and emesis the commonest sign occurring in more than a third of the patients [64]. Fish allergy is usually persistent for life with the exception of one case report [65]. Tuna is extensively consumed, and many fish-allergic individuals are able to tolerate canned tuna. Cod and herring are a popular choice for fried fish, and mackerel and salmon are also commonly used in mainstream cooking. Extensive cross reactivity between different species of fish including freshwater and saltwater fish has been demonstrated. Parvalbumin (Gad c1), a small protein, is the major allergen in fish, which is extremely resistant to heating and digestive enzymes. Diagnosis of fish allergies can become very simple with the characterization of recombinant carp parvalbumin rCyp c 1, which contained the majority of the IgE epitopes present in natural extracts of tuna, cod, and salmon and reacted with IgE from all the fish-allergic patients that were tested [66].

Allergy to crustaceans such as shrimp, lobster, crab, and crawfish is also very common with similar potentially fatal reactions. Seafood allergy is generally lifelong. There is extensive cross reactivity between crustaceans [67]. However, crustaceans do not cross react with vertebrate fish. Tropomyosin, a muscle protein, is the major allergen in crustaceans. It is found in mollusks, and is seen in arthropods such as dust mites and cockroaches, and insects such as grasshoppers [68, 69]. Vertebrate tropomyosins are nonallergenic. Other reactions to seafood include delayed GI reactions to oysters and clams. Handling seafood has been reported to cause occupational asthma and contact urticaria.

Allergies to Vegetables and Fruits

Allergic reactions to fruits and vegetables are common in both adults and children, where the consumption is high in Europe. Cross reactivity between fruits and vegetables are uncommon, however, cross reactivity is observed between pollens and fruits. Ragweed-allergic patients are allergic to melons and bananas, and birch allergy is often associated

with allergy to apples. Latex allergy is associated with allergy to melons, banana, kiwi, avocado, and chestnut [70].

The oral allergy syndrome presents with oropharyngeal pruritis, tingling, and/or edema soon after eating certain fresh fruits and vegetables. Fruits commonly associated with the oral allergy syndrome are peach, nectarine, and members of the Rosacea family. Seasonal exacerbation of symptoms may occur or the symptoms may only present if the fruit is eaten during pollinosis of a cross-reacting tree or plant. Symptoms are usually self-limited and usually do not require treatment, however, severe systemic reaction have been reported in 1% to 2% of patients. Reactions usually do not occur if the fruit is cooked or peeled. The allergen is thought to be concentrated under the peel and is usually heat labile. Skin testing to commercial extracts may be negative, therefore, fresh fruits are used and the patient is tested by the "prick and prick" method. Lipid transfer proteins, the universal plant pan allergens, are thought to be responsible for these reactions [71]. Other pathogenesis-related proteins such as Thaumatin-like proteins are also involved [72]. Conventional immunotherapy for allergic rhinitis may help with pollen food allergy syndrome, although further studies are needed.

Seed Allergies

Reactions to seeds, although anecdotal, have been reported to be life-threatening. Sesame allergy is prevalent in Israel [73] and the Middle East and is increasingly being reported in the UK [74]. Reactions to mustard, poppy, and sunflower have been reported and confirmed by double-blind challenges. Anaphylaxis to cottonseed, dill, poppy, coriander, flaxseed, and caraway has been reported. Cottonseed oil, flax seeds, poppy seeds, and caraway are used in baked goods. Sesame, black mustard, poppy seeds, fennel, anise, caraway, and coriander are used in different ethnic cuisines. Seed storage proteins have been implicated in some of these reactions [15]. These proteins are usually stable, heat-resistant, and can cause systemic reactions even in trace quantities.

Atopic Dermatitis

Food allergy is responsible for 30–40% of atopic dermatitis in children <5 years of age [75]. Therefore, carefully evaluating these patients for food allergies is essential as elimination of the offending food often results in a dramatic improvement in many infants and young children. Food-specific IgE levels may be very useful in ascertaining whether or not these children are truly allergic as they generally have elevated IgE levels; besides skin tests may be difficult to perform in some of these children. Food-specific IgE levels for foods other than milk, egg, and peanut must be interpreted with caution. Improvement of symptoms must be clearly documented if any food is withheld on the basis of skin testing or IgE results.

Children with atopic dermatitis were followed-up regularly from infancy to age 7 to look at the risk factors for sensitization to food and airborne allergens [76]. In this cohort, reactions to milk and eggs (as documented by positive skin tests) were transient but reactivity to peanuts was persistent. Sensitization to aeroallergens occurred in 80% with 75% becoming symptomatic. Those with sensitization to egg, early onset of eczema, and a family history of atopic disease were deemed to be at risk.

Food-Induced Contact Dermatitis and Occupational Allergies

Food-induced contact dermatitis has been reported in people handling raw seafood. Baker's asthma is an occupational disease caused by exposure to the wheat allergen. Aerosolized egg protein can cause respiratory symptoms.

Reactions to Food Additives, Dyes, and Preservatives

Although often implicated commonly by patients, allergic responses to dyes, preservatives, and food additives are very rare; most of the reports being anecdotal or isolated case reports with very few controlled studies actually substantiating these findings. Reported symptoms vary from mild to severe with the manifestations being anaphylaxis, urticaria, angioedema, and/or asthma. This section has been summarized from the outstanding review article by Simmons [77].

Sulfites have been shown in well-controlled studies to induce severe bronchospasm and life-threatening asthma episodes in sulfite-sensitive individuals. Sulfite-sensitive asthma affects 5% of the asthmatic population with symptoms ranging from mild to severe. The exact mechanism is not clear but is thought to be because of the inhalation of the sulfur dioxide generated in the oropharynx. Low levels of sulfite oxidase, the enzyme responsible for the conversion of sulfites to sulfates, have been implicated in some of the patients with severe reactions to sulfites. Some investigators have demonstrated an IgE-mediated response. Sulfites have been used to prevent enzymatic browning of fresh fruits and vegetables such as apples and potatoes. Nonenzymatic browning in dried fruits; dehydrated vegetables, in particular, potatoes; wines;

and vinegar are prevented by adding sulfites. Sulfites are used as sanitizers for food containers and are added to food to prevent spoiling because of their antimicrobial actions. They are also used to inhibit the growth of undesirable microbes during the process of fermentation, and their antioxidant effect enhances the flavour of beer. The FDA has banned the use of sulfites in fresh fruits and vegetables, which had been used extensively in salad bars. High levels of sulfites are found in dried fruits such as golden raisins and apricots, wine, nonfrozen lime/lemon juice, sparkling grape juice, sauerkraut juice, molasses, and moderate levels in dehydrated potatoes, certain pickles, fruit toppings, pectin, gravies, white vinegar, and fresh shrimp. Low levels (<10 ppm), which are found in a wide variety of foods including beer, soft drinks, dough conditioners, baked goods, jams, and jellies, have not shown to cause reactions.

Dyes approved by the Food Dye and Coloring Act (FD&C) include tartrazine (FD&C yellow no. 5), sunset yellow (FD&C yellow no. 6), erythrosine (FD&C red no. 3), ponceau (FD&C red no. 4), brilliant blue (FD&C blue no.1) and, indigotin (FD&C blue no. 2). Amaranth (FD&C red no. 5) has long since been banned in the United States because of implications of carcinogenicity associated with its use.

Monosodium glutamate (MSG) is known to cause the Chinese restaurant syndrome, which presents with a symptom complex which includes chest tightness, a burning sensation at the back of the neck, nausea, diaphoresis, and headache occurring within hours of ingestion. Although declared on food labels by FDA mandate, the exact quantity is usually not declared. Reactions have been demonstrated to be dose-dependant with some preparations containing considerable amounts of MSG.

Aspartame, a low-calorie sweetening agent, is used in beverages. Nitrites and nitrates are used as preservatives and also as flavoring and coloring agents in processed meats. Double-blind placebo-controlled challenges have failed to demonstrate urticaria and/or angioedema with sulfites, tartrazine, MSG, or nitrites.

Butylated hydroxyanisole (BHA) and butylated hydroxytoulene (BHT) are used extensively as preservatives in cereals. DBPC has demonstrated the association of chronic urticaria with these agents in a well-documented report.

Natural food additives used commonly are annatto, carmine, saffron, and erythritol. Annatto is extracted from the fruit of the tropical tree *Bixa orellena*. It is used to impart the yellowish orange color to foods such as popcorn, and beverages. Saffron, derived from the flower *Crocus sativa*, is both a coloring and flavoring agent used in cakes, sauces, rice preparations, curries, and deserts in Indian, Spanish, and Middle Eastern cooking. Carmine is natural red dye derived from the dried bodies of the females of the American insect *Cocus cacti* and is used extensively in beverages, candy, ice creams, confectionery, jams, jellies, caviar, cheese, butter, and delicatessen meats. These agents have the potential to cause anaphylaxis because of their protein content, and there have been several case reports to this effect.

Diagnosis

Obtaining an accurate history is the key element in the diagnosis of food allergies. The exact nature of the symptoms, relationship between the timing of food ingestion and the onset of symptoms, and reproducibility of the reactions must be elicited. Dietary details are crucial, and a symptom diary noting the relationship of the ingestion of different foods to the symptoms is very helpful. Reading labels and speaking to people who have actually prepared the food is very crucial in identifying "hidden ingredients" and cross contamination with known allergens. If necessary, the manufacturer should be called to get further details. It is important at the outset to distinguish between food intolerance versus an allergic reaction, and furthermore, if the allergic reaction is an IgE- or non-IgE-mediated response. The potential severity of the response must also be assessed.

Skin Testing

Skin tests should only be done by qualified personnel in settings which are equipped to treat anaphylaxis. Percutaneous or prick skin tests are performed. Intradermal tests are not recommended for foods because of the risk of systemic reactions and possible nonspecific irritant responses. Extracts are selected based on a careful history, which narrows down the possible etiology to a few foods. Testing randomly with a standard panel of different foods is not indicated as 50% of the time a false positive reaction can occur. A negative reaction essentially excludes the IgE antibody in over 95% of the cases. Negative reactions could also occur with commercial extracts of fruits and vegetables, hence, they might have to be repeated with fresh extracts.

If there is a history of a related anaphylactic reaction, then a skin test is not usually performed, the food-specific IgE test is initially done as a screening test instead. Skin tests may not be able to be performed in patients with severe atopic dermatitis or in patients with certain clinical conditions such as autism or if they have an antihistamine on board. They are negative in 50% of the patients with eosinophilic GI allergic disorders. Some patients with eosinophilic GI disorders show positive responses to patch tests, however, patch tests for foods are not yet standardized for food allergens. Specific wheal sizes to different foods and the risk of positive challenges have been determined. A wheal of >8 mm has been found to correlate with a positive

challenge in children with peanut and tree nut allergies (In children below a year of age the wheal dimension is much smaller).

IgE concentrations and prick skin tests may provide additional information about the likelihood of outgrowing a specific allergy over time [78]; however, there is considerable variation in the technique of performing these tests.

Food-Specific IgE Measurement

Measurement of food-specific IgE antibodies in the patient's serum is of enormous value in diagnosing food allergies. They are more reliable than the conventional RAST testing in predicting clinical reactivity. However, they must be done in reliable laboratories using standardized assays such as CAP Systems FEIA, Pharmacia-Upjohn Diagnostics (CAP FEIA). The values predict the probability of reacting or not to the food in question and should be performed once the suspected foods have been narrowed down by history. However, it is important to note that false positive and false negative tests can occur. These tests are useful both for the initial screening, diagnosis, and can also be used for prospectively following-up the sensitivity of a patient. Randomly performing food-specific IgE tests to panels of foods are not clinically indicated and may be misleading, as very often, patients perceive anything above 0.35 kU_A/l as "positive". Tests to peanuts, nuts, fish, shellfish, egg, and milk are better standardized and have acceptably accurate predictive values compared to other foods. Food-specific IgE levels and the cut off value kU_A/l have been determined to avoid food challenges. A level above 7 kU_A/l for egg, 14 kU_A/l for peanut, 15 kU_A/l for milk and 20 kU_A/l for fish suggest a high likelihood of reacting clinically, hence, oral challenges are unnecessary and may even be dangerous [79]. Younger children have lower predictive values. In children <1 year of age, there is a 95% chance of reacting to milk and in children <2 years, there is a 95% chance of reacting to egg at a level >2 kU_A/l [80]. Reactions are unlikely for levels <0.35 kU_A/l. If, however, the history of the reaction is convincing but the levels are <0.35 kU_A/l and the skin test is also negative, then an oral challenge is warranted. For children with possible reactions to egg, milk, or peanut, it has been suggested that oral challenges can be safely performed at (CAP-FEIA) levels of <2 kU_A/l for egg, <2 kU_A/l for milk, and <2 kU_A/l for peanut with a history of reactions and <5 kU_A/l for peanut with no clinical history of a reaction [81]. Results for wheat and soy were not as clear, and it was found that concomitant eczema or asthma was associated with failed egg challenges. This study was done in highly allergic children at a median age of 4.8 years referred to a tertiary care allergy center. Physician-supervised challenges in settings equipped to deal with anaphylaxis must be done when there is a history of systemic symptoms and/or the suspected food in question is highly sensitizing, for example peanuts, tree nuts, fish, and shellfish.

Newer Diagnostic Methods

Protein microarrays have the ability to detect specific allergenic epitopes from individual food proteins and have revolutionized the management of food allergy [28]. Food-specific IgE tests are limited by the fact that the food-specific IgE levels fall in the in between range. Also, accurate cut off points have not been established for several foods. Oral food challenges although the gold standard are time consuming and do carry the risk of precipitating anaphylaxis in sensitive patients. Microarrays have the ability to detect several allergenic proteins simultaneously and require very minute quantities of blood (50 μl) in children. Above all, they also have the ability to predict the likelihood of persistence of allergy to a particular food by identifying the nature of the epitope as IgE against some of these specific epitopes that are more likely to be associated with persistence than others. The exact structure of the allergenic proteins should be known. Sequences of major allergens for peanut, milk, egg, and fish have been determined with tree nuts and seeds being sequenced more recently. Individual allergen microarrays have been used to assess IgE-mediated reactions [81]. Recombinant or purified allergen molecules were spotted on glass slides to provide allergen chips. Peptide microarrays assay is the latest innovative technique in determining specific IgE-binding epitopes [24]. Advantages include rapidity of the assay and the minute quantities of sera required. These techniques are being used in research laboratories and are not yet commercially available.

Food Challenges

Oral food challenges are performed when the skin tests and food-specific IgE tests are negative and the patient still complains of problems with a particular food or if the initial history was that of anaphylaxis. The food is fed to the patient in gradually increasing doses and the patient is carefully observed to see if the symptoms are produced. This procedure should be done by qualified personnel and in facilities, which can handle anaphylaxis, and can either be an open challenge, single blind or double blind. The gold standard for diagnosing a food allergy is a double-blind placebo-controlled challenge, although in clinical practice, especially in infants, open or single blind challenges are quite useful. Open or single blind challenges could be done as an initial screen if several foods are suspected.

There are a number of unproven tests such as provocation neutralization, cytotoxic tests, applied kinesiology, hair analysis, and IgG_4 testing.

Elimination Diets

Elimination diets are an essential component for diagnosing food allergies in some patients when skin tests and food-specific IgE tests are unable to identify the food in allergic eosinophilic GI disorders. The suspected causative food is eliminated for a period of about 6 weeks and the patient is observed to see if the symptoms are resolved. It is important to completely eliminate the offending food and to carefully read labels or examine the ingredients of all the foods eaten both in the house, outside, and while using processed or ready made foods. When multiple foods are suspected, the patients should be given a strict diet to follow. If symptoms resolve, one food at a time is reintroduced in an attempt both to liberalize the diet and to correctly identify the inciting foods. In complicated cases, an elemental diet using a hydrolyzed or elemental amino acid-based formula is used.

Natural History

The clinical course and the natural history of food allergy depend on the type of the clinical response, and particularly, the molecular characteristics of the causative food protein. Approximately 85% of the children with IgE-mediated allergies to milk, egg, soy, and wheat outgrow their allergies by age 3. In contrast, allergies to peanut, nuts, and seafood are usually lifelong. Recent data has shown that 20% of children with peanut allergies, a small percentage of tree nut-allergic, and even a few reports of fish-allergic children may outgrow their sensitivities. Adverse reaction to fruits and vegetables and cereal grains other than wheat are also short-lived. Therefore, children should be repeatedly reevaluated to see if they have outgrown their allergies, in addition to the history, periodic food-specific IgE tests, and/or skin tests should be performed annually to assess for persistence of sensitivity. It is not very clear if total avoidance of the specific food increases the chances of outgrowing the allergy or if the introduction of small amounts increases tolerance.

Management

Allergic disease must be distinguished from nonallergic diseases based on a detailed history and physical examination. Inadvertent exposure and hidden ingredients in foods prepared by caterers and at restaurants pose a bigger risk to patients; therefore, a detailed history is critical in determining the etiology of the not so obvious reactions. If an allergic disease is suspected, skin tests may be performed. Testing should be performed judiciously by carefully narrowing down the list of foods based on the history. In case of a history of anaphylaxis, food-specific IgE test is first performed; if negative, a skin test is performed. The food may be reintroduced into the diet if the tests are negative. If the history is convincing, particularly of a serious reaction, then a physician-supervised challenge is performed in those patients with negative skin and food-specific IgE tests. Patients with positive tests are asked to strictly avoid the food and monitored for resolution of symptoms. If the symptoms do not resolve with the elimination diet, then the food is reintroduced, unless, again if a convincing history warrants a supervised food challenge. Open or single blind challenges are performed initially with double-blind placebo-controlled challenges reserved for equivocal oral challenges.

Because there are no specific laboratory tests for non-IgE-mediated disease, the diagnostic approach rests on elimination diets and oral challenges. Persistence of symptoms despite an elimination diet rules out food allergy. This approach can be used for complaints such as headaches, behavior, etc., which are not classically associated with foods. If elimination diet results in the resolution of symptoms, oral challenge is performed to identify the specific food involved. In many cases of eosinophilic GI disorders, endoscopic biopsy (to evaluate for eosinophilic infiltration) may be required to confirm the diagnosis.

Dietary Elimination

Dietary elimination is very challenging to implement. Care should be taken to avoid inadvertent exposure and also to make sure that the food in question is not a “hidden ingredient” in a common preparation. For example some ice creams contain eggs; an egg allergic patient may eat the ice cream without realizing that egg is one of the ingredients. Another practical issue is cross contamination, which can occur if equipment is shared while manufacturing or cooking food. Care should be taken that the diet is nutritionally adequate, especially with multiple allergies. The Food Allergy and Anaphylaxis Network is an excellent resource for patients and their care givers (http://www.foodallergy.org or 1-800-929-4040).

Follow-Up

As many of the food allergies are outgrown, periodic reevaluation is indicated.

Prevention of Food Allergies

Sensitization of the fetus can occur in utero, besides, allergenic proteins have been shown to pass into breast milk [82]. Infants with a strong family history of atopy,

particularly parental asthma, are at risk for developing food allergies. There is no substantial evidence that avoidance of highly allergic food allergens during pregnancy and lactation decreases the risk of developing allergic disease. In fact, avoidance of multiple food allergens may compromise the nutritional status of the mother and infant. Although studies have generally showed decrease in the severity and a delay of the onset of atopic dermatitis and food allergies by dietary restriction of highly allergenic foods, these differences have not shown to be persistent and some studies have not showed a protective effect. Many of the earlier studies are fraught with methodological flaws including recruitment and reporting bias, confounding factors, inability to randomize, and particularly, the inability to determine whether or not the infants were exclusively breast fed along with the exact duration of breast-feeding [83].

Prolonged breast-feeding and the delayed introduction of solids appear to confer a protective effect [84]. It is not very clear if feeding infants cow's milk formula in the first few days of life or the use of soy as supplementation places them at risk. The use of extensively hydrolyzed elemental formula in conjunction with the avoidance of milk-based formula and delaying the introduction of solids till 4 months of age in a prospective study done in high-risk infants showed a significant decrease in the cumulative incidence of eczema, food allergy, and in particular, cow's milk allergy till age 4 [85]. Two other prospective studies also showed a significant decrease in the cumulative incidence of cow's milk allergy and food allergy till age 5 and 7 years [86]. Partially hydrolyzed formula has shown a protective effect but not as much as the extensively hydrolyzed formula [87, 88].

The American Academy of Pediatrics (AAP) recommends, based on consensus, the avoidance of peanuts during pregnancy and a consideration of avoiding other allergenic food such as milk, egg, and fish during lactation for infants at risk [53]. Infants at potential risk are defined as those with either a parent or sibling with allergies. Exclusive breast-feeding is recommended for 6 months to 1 year, and supplementation, if required, with an extensively hydrolyzed or preferably an elemental formula. Further, the AAP recommends, in these infants, that the introduction of solid foods should be delayed for 6 months and cow's milk to 1 year of age, eggs to 2 years, and peanuts, nuts, and seafood to 3 years.

The European Society of Pediatric Allergy and Clinical Immunology (ESPACI) and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), in their joint position statement [89], do not recommend any dietary restrictions during pregnancy and lactation, but advocate exclusive breast-feeding for at least 6 months, supplementation, if necessary, with a formula of documented hypoallergenicity along with delayed introduction of solids till 4 months.

Intestinal microflora has been though to play a critical role in the development of food allergies. Antenatal supplementation with probiotics in mothers of high-risk infants showed a decreased rate of developing atopic dermatitis [90].

The Section on Pediatrics, European Academy of Allergology and Clinical Immunology have made recommendations for high-risk infants based on the evidence from a comprehensive review of the literature by an international group of food allergy experts, which are summarized in the following statements. Exclusive breast-feeding for 4 to 6 months with introduction of solids at 4–6 months, along with supplementation with an extensively hydrolyzed formula for 4 months if required in atopic infants (cow's milk formula may be used in nonatopic infants) [91].

Newer Therapies

Traditional Chinese herbs have shown promising results in a murine model of peanut anaphylaxis [92]. Treatment of highly peanut-allergic patients with anti-IgE antibodies (TNX-901) did show some, albeit small improvement in the average amount of peanut tolerated, but 25% of the patients showed no response [93]. Novel techniques such as induction of tolerance are still being studied.

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