# Clinical Aspects of Pediatric Food Allergy and Failed Oral Immune Tolerance

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**Abstract:** Food allergy seems to represent a new spectrum of disease that has elicited significant community concern and extended waiting lists for allergists and gastroenterologists alike. The apparent rise in prevalence of IgE-mediated food allergy (and associated risk of anaphylaxis) has been postulated to result from effects of a "modern lifestyle" but as yet clear environmental risk factors have not yet emerged. Family history seems to contribute to risk suggesting that gene–environment interactions will be important for identifying a subpopulation with increased susceptibility to any identified lifestyle effects. Non-IgE-mediated food allergy (including food-induced enteropathies and colitides, eosinophilic esophagitis, and Crohn's disease) with potentially similar environmental triggers resulting in diverse immune dysregulatory mechanisms. The evidence underpinning the putative rise in food allergy is discussed and potential mechanisms of disease explored. Clinical aspects of various food allergic conditions including non-IgE-mediated food allergy are outlined.

**Key Words:** food allergy, prevalence, enteropathy

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Childhood food allergy is now a major public health problem and seems to be increasing in industrialized countries.[1] Both prevalence figures and the spectrum of food allergens vary considerably between geographical regions and are thought to reflect the variation in diet between different cultures.[2] It is estimated that about a quarter of the population will have an adverse reaction to food (of which food allergy is just one type) during their lifetime,[3] especially during infancy and early childhood. An estimated 10% to 15% of children report symptoms of food allergy, although the prevalence of immunoglobulin class E (IgE)-mediated food allergies [ie, symptoms of food allergy in the context of a positive skin prick test (SPT)] is reported to be lower, at approximately 6% to 8%.[4] By contrast, not much is known about prevalence of non-IgE-mediated food allergies although both eosinophilic esophagitis (EE) and celiac disease have been documented to be on the rise.[5–10]

There has been a significant increase in public awareness of food allergies, as highlighted in media reports owing to the concerning increased prevalence of the most serious manifestation of food allergy, anaphylaxis. However, some medical practitioners remain sceptical about the role of food allergies in a number of clinical syndromes, such as atopic dermatitis, colic, and gastroesophageal reflux in infancy, despite an increasing body of evidence that food allergy can contribute to these conditions.[11] There has been a significant amount of research attempting to delineate the role of foods in either precipitating or aggravating irritable bowel syndrome in adults [reviewed in[12]], but this work is outside the scope of this review.

## WHAT IS FOOD ALLERGY?

Allergic reactions to foods result from the inappropriate development of a robust immune response against one or many specific food antigens. In this way, food allergy is distinguishable from other types of food sensitivity, such as intolerances and malabsorption syndromes (eg, lactose malabsorption), pharmacologic reactions to food components (eg, vasoactive amines), and food-borne infections and poisonings. Food allergy is often described separately from celiac disease, which involves immunologic reactions to both food-derived protein and self-antigens located in the gut, although the main reason for the distinction is more likely to be due to the fact that celiac disease is seen within the clinical domain of gastroenterologists rather than allergists.

## WHAT ARE THE KNOWN MECHANISMS OF FOOD ALLERGY, AND HOW DO PATIENTS PRESENT?

Food allergies can be broadly divided into 2 types: those mediated by food-specific IgE antibodies and those that are not (Tables 1, 2). Of the 2, much more is known about IgE mediated than non-IgE-mediated food allergy.

## IgE-MEDIATED FOOD ALLERGY

IgE-mediated food allergy is characterized by immediate reactions to food in the context of a positive SPT, including urticaria, vomiting, angioedema, and/or anaphylaxis within 1 to 2 hours of ingestion of the offending food. Symptoms of such allergies usually begin within the first 2 years of life, often after the first known exposure to the food and onset later in life is unusual.[13,14]

Although, in theory, any food protein may have the ability to sensitize the immune system, more than 90% of IgE-mediated food allergies in children are caused by just

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**TABLE 1.** Distinction Between IgE-mediated and non-IgE-mediated Food Allergy

| Acute Allergic Reactions IgE | Intermediate Mixed | Delayed Allergic Reactions Non-IgE |
|---|---|---|
| Time to onset of reaction | | |
| < 1 h | 1–24 h | > 24 h |
| Volume required for reaction | | |
| Small | Moderate | Large |
| Symptoms | | |
| Urticaria | Vomiting, | Diarrhea |
| Angioedema | Diarrhea | Eczema, |
| Vomiting | | Failure to thrive |
| Anaphylaxis | | Gastroesophageal reflux |
| Oral allergy syndrome | | Severe irritability |
| Eczema | | Food impaction |
| Immune profile | | |
| Class: IgE mediated | Class: Mixed IgE mediated and non-IgE mediated | Class: Non-IgE mediated |
| Characteristics: skin prick test wheal/elevated levels of food-specific serum IgE antibodies | | |

Modified from Allen KJ, Heine R, Hill DJ. *MJA*. 2006;185:394–400.

8 food items: cow's milk, soy, hen's egg, peanuts, tree nuts, wheat, fish, and shellfish. Typically, food allergens are glycoproteins that are relatively resistant to digestion and cooking. A large number of food allergens have now been identified and characterized including β-lactoglobulin in cow's milk,[15] ovomucoid (Gal d 1) in egg,[16] and *Arachus hypogaea* allergens 1 and 2 in peanut.[17] On each of these proteins, specific epitopes (structural components of the antigen molecule) have been mapped that interact with food-specific IgE antibody or T-cell receptors. Further characterisation of these epitopes will be essential for developing food vaccines or genetically modified hypoallergenic foods. Epitopes also seem to have a prognostic role in food allergies. Linear epitopes are typically associated with long-term, persistent allergies, whereas conformational (3 dimensional) epitopes may be associated with more transient allergies.[18]

One of the commonest forms of food allergy in adults, which can also present in adolescence although rarely in younger children, is the oral allergy syndrome. In sensitized individuals, cross-reactions between pollens and foods such as fruits, vegetables, and nuts can result in an immediate allergic reaction involving swelling confined to the mouth and tongue after ingestion of the food. As a form of IgE-mediated food allergy it has been reported to be associated with anaphylaxis although this seems to be uncommon.

In IgE-mediated food allergy, specific IgE antibodies, when encountering the food, are able to trigger mast cell degranulation, resulting in local release of histamine and other mediators that promote edema, erythema, and itch. In its most severe form, an IgE-mediated reaction can result in anaphylaxis, a multi-system reaction involving the respiratory and circulatory systems which can be fatal if not treated with intramuscular adrenaline.

Identification of people at risk of IgE-mediated food allergy is achieved through detection of food-specific IgE. SPT is a readily available and inexpensive means of testing whether a food protein is able to trigger local edema (a wheal) and erythema (flare) through a tiny breach in the skin. SPT has a high negative predictive value, allowing reassurance that a clinical reaction is highly unlikely given a negative test.[19] However as the test has a low positive predictive value (ie, some people with a positive SPT are asymptomatic upon ingestion of the food) clinical evidence of an objective acute allergic reaction (either through formal food challenges or careful history) is central to the diagnosis of IgE-mediated food allergy. The proportion of people that test negative to a food with SPT, but are truly reactive to a food, is likely to be $< 1\%$.[20]

Food-specific IgE antibodies can also be detected in serum, though laboratory reference ranges vary widely.[21,22] Low levels of food-specific serum IgE can be detected in nonallergic people, indicative of a "sensitized" but not "allergic" status. Serum IgE levels should be presented on an absolute scale, in $kU_A/L$, rather than on semiquantitative scales (eg, high/medium/low), as diagnostic decision points are available for several major food allergens.[22]

Diagnostic decision points can be used for both SPT[23] and allergen-specific serum IgE[24–26] but may need to be derived by each centre as both varying methodology and pretest probability based on population prevalence are likely to influence the likelihood that a certain SPT or specific IgE threshold predicts food allergy. These decision points are often referred to as 95% positive predictive values and clinicians use predetermined thresholds (such as 8 mm for peanut) to avoid unnecessary and expensive confirmatory food challenges. Positive predictive values are helpful in predicting likelihood of allergic reaction but are unable to predict severity of reaction which can range from urticaria through to anaphylaxis.

Treatment of IgE-mediated food allergy involves strict allergen avoidance and provision of an adrenaline autoinjector if deemed at high risk of anaphylaxis.

Until recently there have been few data on T-helper cell (Th) cytokine profiles specific to the mechanism underlying food allergy. Past studies have shown that the maturation of interferon (IFN)-g producing T cells and the function of suppresser T cells were delayed in children with a challenge-proven allergy to cow's milk, and normalized when oral tolerance was demonstrated.[27–29] More recent research suggests that there is an increase in regulatory T cells (Tregs) that express the molecule FOXP3 in children who develop tolerance to cow's milk.[30] Genetic defects in the development and function of Tregs, most notably FOXP3 deficiency (the master switch gene for $CD4^+$ $CD25^+$ Tregs), have been associated with a marked increase in the incidence of food allergy such as that occurs in the immune dysregulation polyendocrinopathy enteropathy X-linked syndrome.[31]

Many environmental factors are found to exert their effect on the expression of genes through mechanisms termed "epigenetics." The most commonly described epigenetic modification is the methylation of CpG dinucleotides within sites in an individual's DNA, usually in regions that regulate gene transcription (promoters). There have been few studies to assess the role of epigenetic regulation in the expression of immune mediators of food allergy,although there is evidence to suggest their role in modifying the risk of asthma.[32] Recently Floess et al[33]

**TABLE 2.** Non-IgE-mediated Inflammatory Syndromes Currently Ascribed to Food Allergy

| Syndrome | Age | Symptoms | Causal Foods | Investigations | Treatment | Differential Diagnoses |
|---|---|---|---|---|---|---|
| Food protein-induced enteropathy | Early infancy | Protracted diarrhea, vomiting, abdominal distension, failure to thrive, edema | Cow's milk, soy, egg, wheat, rice, chicken, fish | Endoscopy/biopsy: patchy villous atrophy with cellular infiltrates; medically-supervised home-based elimination/ rechallenge | Elimination diet with hypoallergenic infant formula | Coeliac disease |
| Food protein-induced proctocolitis | First weeks-months of life | Isolated bloody stools, otherwise well and thriving | Cow's milk, soy milk, breast fed (50%) | Rectal biopsy only if atypical features or nonresponsive to treatment(typically findings eosinophils, mucosal edema, ulceration, erosions in distal bowel); medically-supervised outpatient food challenge | Elimination diet with hypoallergenic infant formula | Constipation with fissure |
| Food protein-induced enterocolitis | Young infants | Protracted diarrhea, projectile vomiting, pathognomically 2-4 h postingestion, hypovolemic shock (20%) | Cow's milk, soy milk, rice, beef, poultry, grains (does not occur in exclusively breast fed infants) | Stool samples-occult blood, polymorphonuclear leucocytes, eosinophils, reducing substances; medically-supervised home-based elimination/ rechallenge | Elimination diet with hypoallergenic infant formula | Sepsis, gastroenteritis, malrotation, intussusception, inborn errors of metabolism |
| Eosinophilic esophagitis | Any age (early infancy more diet responsive) | Gastroesophageal reflux postprandial nausea, vomiting, diarrhea, abdominal pain; | Cow's milk, grains, meat (often difficult to determine) | Skin prick test (not reliable), atopy patch testing, medically-supervised home-based food elimination/ rechallenge with biopsies | Elimination diet (usually 6 foods), swallowed or inhaled corticosteroids | Gastroesophageal reflux, mucosal candidiasis |

discovered that expression of FOXP3 in CD4+ CD25+ Tregs needs to be stabilized by complete demethylation of its promoter, without which both FOXP3 expression and its suppressive activity is lost.

## NON-IgE-MEDIATED FOOD ALLERGY SYNDROMES

Table 1 summarizes presenting signs and symptoms of a number of non-IgE-mediated food allergy syndromes.

### EE

EE is a histologic diagnosis characterized by 15 or more intraepithelial eosinophils per high-power field in esophageal biopsy specimens, absence of significant gastroesophageal reflux (normal pH monitoring study), and/or lack of response to proton pump inhibitors.[34] Infants and toddlers usually present with unremitting vomiting and regurgitation, feeding intolerance or aversion, severe irritability, and may develop failure to thrive. Some experts use SPT and atopy patch testing to guide elimination diets,[35] whereas others empirically remove common food allergens (cow's milk, soy, egg, wheat, peanuts, and tree nuts).[36]

When cow's milk protein is implicated in the pathogenesis of EE, an amino acid-based formula is recommended as first-line therapy. Endoscopies are required to monitor response to dietary elimination or challenge which minimizes unnecessary dietary restrictions. In infants and young children who have failed to respond to dietary elimination, consideration is usually given to treatment with swallowed corticosteroid aerosols.[34]

### Food Protein-induced Enteropathy

Non-IgE-mediated enteropathy is characterized by chronic malabsorption owing to small intestinal villous damage and is most often owing to cow's milk or soy. This disorder mainly occurs in formula-fed infants. Celiac disease presents at a similar age (as wheat and formula are both often introduced into the diet around 6 to 8 mo of age) and with similar clinical features which include persistent diarrhea, perianal excoriation, vomiting, abdominal pain,

and failure to thrive. Edema and ascites may be present in severe cases owing to enteric protein loss. Secondary lactose malabsorption is common, and micronutrient deficiencies (eg, iron, folate, and fat-soluble vitamins) can occur. Diagnosis may be delayed in those patients mislabeled as lactose intolerant, because partial improvement may occur on a lactose-free (but cow's milk containing) formula. However, whereas a lactose-free diet reduces the osmotic diarrhea, continued cow's milk protein exposure perpetuates the villous damage.

### Proctocolitis

Food protein-induced proctocolitis is an allergic inflammatory process involving the distal colon and usually presents in the first 3 months of life with low-grade rectal bleeding in an otherwise thriving infant. Cow's milk protein is the most common cause, although other food proteins (eg, soy, rice, wheat) have been implicated[37] and it frequently occurs in breast fed infants as cow's milk β-lactoglobulin and other allergenic proteins are known to be secreted in breast milk.

The majority of breast fed infants with allergic proctocolitis respond to maternal elimination of cow's milk protein, although some require the additional elimination of soy[38] or conversion to extensively hydrolysed formula if unresponsive to dietary elimination within 2 weeks. In refractory cases, transition to an amino-acid based formula may be required. The majority of infants with allergic proctocolitis develop tolerance to cow's milk by 12 months. Monitoring of iron status and hemoglobin is required in infants with prolonged symptoms. Consideration of endoscopic examination is recommended in infants with protracted rectal bleeding or associated complications such as failure to thrive or anemia.

### Food Protein-induced Enterocolitis Syndrome

Food protein-induced enterocolitis syndrome (FPIES) is a curious syndrome and has only been recently described. It is a non-IgE-mediated food allergic manifestation that typically presents in infancy[39] and the most common causes are cow's milk, soy, and rice,[40] but can also be associated with meats and cereals.[41] Failure to recognize FPIES is common and infants may be misdiagnosed as having septic shock, surgical conditions (eg, malrotation or intussusception), gastroenteritis, or inborn errors of metabolism. The following diagnostic criteria have been proposed: (1) repetitive vomiting and/or diarrhea within 4 hours of ingestion (after first exposure to a food) without other identifiable cause, (2) symptoms limited to gastrointestinal tract, (3) complete resolution of symptoms on avoidance, and (4) recurrence of symptoms upon challenge.[41] Hypovolemic shock has been described in up to 20% of cases.[39] There are no useful diagnostic tests for FPIES, and the diagnosis relies on recognition of clinical features. The role of atopy patch testing and SPT in FPIES is unclear,[41,42] although SPT is often undertaken to exclude IgE-mediated cow's milk protein allergy.

Treatment involves a strict cow's milk-free diet and usually replacement with extensively hydrolyzed formula because of the common association of cow's milk FPIES with soy FPIES.[43] FPIES has not been reported in exclusively breast fed infants and no maternal elimination of cow's milk protein is necessary while breast feeding. Diagnostic challenges for FPIES should be deferred until 2 to 3 years of age at which time FPIES is most likely to have resolved. Some centers obtain intravenous access before a challenge owing to the risk of hypovolemic shock. There are no published food challenge protocols for FPIES, and challenges should only be undertaken by clinicians experienced in their administration.

## IS FOOD ALLERGY ON THE RISE?

The prevalence of IgE-mediated food allergies seems to be increasing in industrialized countries after the previously documented rise in prevalence of other atopic conditions such as asthma, eczema, and allergic rhinitis,[44–47] although reliable, population-based data are limited. Recent studies have tried to confirm anecdotal evidence of an increased incidence of peanut allergy. In a UK study, Grundy et al[48] found an increase in reported peanut allergy from 0.5% to 1.5% in 2 sequential early childhood cohorts from the same geographic area, surveyed 6 years apart. However, the difference did not reach statistical significance ($P = 0.20$), perhaps owing to lack of numbers or because the number of years between measurement points may have been insufficient to demonstrate an increase in allergy.

Between 2 United States wide phone surveys, the prevalence of self-reported peanut and/or tree nut allergy increased from 0.6% to 1.2% between 1997 and 2002 among children, though no change was observed for adults.[1,49] In a more recent Canadian study, the prevalence of peanut allergy was found to be stable between 2000 to 2002 [1.63%, 95% confidence interval (CI) 1.30%-2.02%] and 2005 to 2007 (1.50%, 95% CI 1.16%-1.92%).[50] Reliable surveillance of allergy prevalence within populations will be required to measure any future rise in food allergy prevalence.

Examinations of hospital records have been used in an attempt to assess prevalence of more serious allergic reactions. Poulos and colleagues[51] found a continuous increase in the rates of hospital admission for angioedema (3.0%/y), urticaria (5.7%/y), and, importantly, anaphylaxis (8.8%/y), over a 10-year period from 1993. A 5-fold increase in food-induced anaphylaxis among children under 5 years of age was a notable finding, and parallels the findings from population-based prevalence studies.[1,48]

Enteropathy resulting from cow's milk is one of the better understood non-IgE-mediated food allergies. One prospective cohort study of newborns in Denmark found that the incidence of cow's milk enteropathy was 2.2% over the first year of life, with a high rate of resolution (97%) by 15 years of age,[52] however, there are no reports concerning change in prevalence over time. Recent reports suggest a rapid rise in EE[6,53,54]—a condition that was first linked to food allergy in 1995.[55] Celiac disease is also reported to be rising in prevalence[8–10] although there are some suggestions that improved serologic screening studies have increased the case finding for this disease which has a reported prevalence of 0.5% to 1.0% of the community.[56,57]

## WHAT IS THE CAUSE OF THE RISE IN IGE-MEDIATED FOOD ALLERGY?

It is clear that the rise in incidence in food allergy is driven by potentially modifiable environmental factors, as the rise is more rapid than genetic deviation would allow. It also seems that these factors are linked to the "modern lifestyle," as food allergy is more common in developed

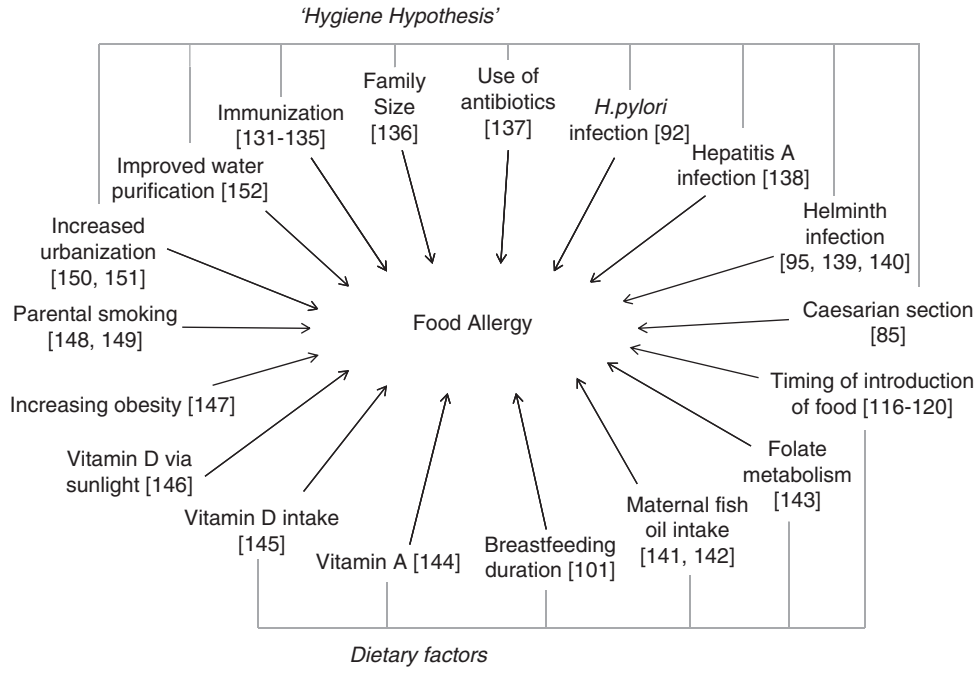


**FIGURE 1.** Potential factors contributing to an increase in IgE-mediated food allergy. The factors listed constitute changing trends over the last few decades, preceding or coinciding with an increase in allergic disease. Evidence for or against a link to IgE-mediated food allergy or food sensitization are provided where available, or else research of the relationship with related atopic manifestations.

than developing countries, and migrants seem to acquire the incident risk of allergy of their adopted country.[58]

Associations have been found between several environmental factors and the development of eczema and atopy, but these factors have not all been formally examined in association with food allergy, despite the strong association between eczema and food allergy.[59,60] Environmental factors associated with the hygiene hypothesis (ie, the hypothesis that early exposure to microbial antigens promote healthy immune development and reduces the risk of developing allergies) and linked to allergic outcomes such as asthma or allergic sensitization include: companion animal ownership,[61] number of siblings,[62] and exposure to farm animals.[63] Timing of allergenic food introduction,[64] timing of introduction of solids,[65] and breast feeding regimes[66] have also been examined, but results were conflicting, possibly contaminated by reverse causation.[67]

Factors associated with a modern lifestyle include a myriad of changes to our level of public health including improved sanitation, secure water supplies (with associated decreased prevalence of *Helicobacter pylori* infection), widespread use of antibiotics and increasing rates of immunization, improved nutrition, decreased helminthic infestation, improved food quality (and presumably less microbial load in the food chain), as well as generally improved nutrition and associated obesity (Fig. 1). These factors might work individually or in concert to effect a failure in the development of oral immune tolerance in the first year of life when development of IgE-mediated food allergy is most likely to occur. The change in prevalence of these factors has all occurred in the last half of the 20th century and yet the rise in food allergy prevalence appears in the context of the early part of the 21st century. If the hygiene hypothesis is found to be central to the rise of both atopy in general and food allergy more specifically this effect might be expressed through a delayed generational effect and the impact of maternal epigenetic modification on fetal priming of the immune system.

## Failure of Development of Oral Immune Tolerance

Environmental risk factors for food allergy will likely affect the induction of immune tolerance to a specific food or the subsequent immune responses that develop after a failure to develop immune tolerance. The ability to distinguish immunologically between self and non-self cells mainly develops in early life, though it is a lifelong process. Therefore, research into these mechanisms in the first year of life in particular is important, if we are to understand the lifelong predisposition to an allergic phenotype.

The process of tolerance development affects the maturation of naïve T cells (Th0 cells) which are directed to differentiate into Th1 or Th2 cells upon exposure to antigens. There is evidence that allergic and nonallergic individuals have contrasting immune profiles, with atopic disease associated with a skewing of the immune system away from a Th1 interferon-gamma (IFN-g) profile toward a Th2 [interleukin (IL)-4, IL-5, IL13] profile.[68] Elevated levels of Th2 cytokines and reduced levels of Th1 cytokines have been consistently demonstrated in subjects with allergic disease[69–73] and, in regard to eczema, the degree of this imbalance has been shown to correlate with disease severity.[70]

Although previous studies have implicated an imbalance of Th1 and 2 cytokine production as predictors of

persistence or development of allergic disease, there is very little population-based data describing the immune profile of food allergic versus nonfood allergic individuals. Decreased IFN-g production at birth is associated with an increased risk for development of general atopic disease (not specifically food allergy) in the first years of life[71,74] and has been reported in newborns with increased familial risk of atopic disease[75] although most studies have used eczema as an outcome. Other studies have suggested that elevated IL-4 serum levels are associated with allergic disease in infancy.[76] Furthermore, normalization of IFN-g production has been associated with resolution of asthma in middle age, whereas persistence of defective IFN-g production was associated with persistence of asthma.[69]

A multitude of factors have been postulated to result in aberrant immune tolerance including: development of abnormal commensal enteric microflora (either reduced biodiversity of flora or colonization with ''bad'' bacteria), dietary factors (insufficient breast feeding, incorrect timing of introduction of solids, or allergenic foods), abrogated gastric acid production (through proton pump inhibitor administration), and maturational delay in intestinal epithelial tight junctions.

## Changes in Commensal Enteric Microflora

IgE class antibodies are part of a Th2-biased immune response, thought to have evolved to deal with persistent parasitic infections. In the course of encountering millions of microbes and molecules in the gut, the mucosal-associated immune system limits or negatively regulates immune responses to those which are not inherently dangerous in a process termed oral tolerance. The development of an inappropriate immune response to food antigens is believed to be due to a breakdown in the process of oral tolerance.

The maturation of the mucosal immune system is prompted by exposure to microbes after birth. In searching for explanations for food allergy, attention has been turned to the composition and timing of exposure to gut microflora, and their possible role in disease development or prevention. Recent research suggests that toll-like receptor-dependent signals provided by intestinal bacteria may inhibit the development of allergic responses to food antigens via stimulation of Tregs, a key player in the induction of oral tolerance.[77] One hypothesis to explain the increased incidence of sensitization to food allergens is that the reduction in early childhood infections or in exposure to microbial products (eg, endotoxin) may impede the development of early immunoregulatory responses. This leaves the immune system more susceptible to inappropriate reactivity to innocuous antigens, resulting in an ''allergic'' reaction.[78]

Postnatal development of mucosal immune homoeostasis is influenced by the type of commensal microflora present in the neonatal period. It has been hypothesized that the predominance of bifidobacteria in breast fed infants may be protective against food allergy, as differences in the neonatal gut microflora between exclusively bottle and breast fed infants precede the development of atopy.[79] This has led to the hypothesis that probiotics may promote oral tolerance. Perinatal administration of *Lactobacillus casei* GG has been reported to reduce the incidence of atopic dermatitis, but not food allergy, in at-risk children during the first 4 years of life. However the topic has remained controversial, with some studies finding consistent results,[80] others failing to find evidence of a protective effect,[81] and yet another finding a protective effect in the context of a caesarean section birth.[82]

After sampling microflora multiple times from 324 infants starting shortly after birth, Adlerberth and colleagues[83] found no association with the lack of any particular flora and the development of food-specific IgE at 18 months of age. It was found that caesarean section delivery was associated with *Clostridium difficile* colonization, as was a lack of older siblings; both factors that have been found to carry a risk of atopic disease in other studies. Another study did find an increased risk of eczema, recurrent wheeze, and sensitization to at least one food or aeroallergen and colonization of *C. difficile*.[84] A recent systematic review found an association of caesarean section and increased risk of developing sensitization to food (and presumed associated food allergy) although this risk seems to be augmented in those with a family history of atopy.[85]

## The Hygiene Hypothesis

The consideration of the composition of gut flora in childhood is part of a broader etiologic theory, namely the hygiene hypothesis. Avenues of investigation have included occurrence of viral, bacterial and parasitic infections, exposure to endotoxin in particular, exposure to potential sources of infection and, true to the name, exposure to hand washing and general cleanliness.

Several epidemiologic studies have semiquantified exposure to pathogens via environmental circumstances, through assessment of number of siblings, pet ownership, and childcare attendance. A review of the literature in 2000 found that a sibling effect (with higher numbers of siblings conveying a protective effect) existed for eczema, hayfever, atopic sensitization, and asthma and wheeze.[62] The weighted average odds ratio of being atopic by SPT or serum IgE, to food or aeroallergens or both, was 0.62 for 3 or more siblings. The authors concluded, however, that the hygiene hypothesis was not able to explain the association alone, hence there questions are raised as how much in utero influences change susceptibility to allergy. There is a need to examine the sibling effect in confirmed food allergy as well as associated atopic disorders. No association was found between dog or cat exposure during the first year of life and confirmed food allergy in one study, though the number of allergic children considered was small ($N = 15$).[86] A systematic review found a protective effect of cat or dog exposure on eczema at all ages, which in childhood is closely linked food allergy, but it was found to be statistically insignificant when animal avoidance behavior was taken in to account.[87] Daycare attendance was found to be protective against wheeze in later childhood (0.8, 95% CI 0.6-1.0),[88] though this has recently been disputed.[89] Early daycare attendance was found to be a risk factor for nonatopic eczema but not atopic eczema, raising the possibility that daycare may be protective against persistence or development of sensitization.[90] Research into the effect of daycare on food allergy is lacking, and care must be taken to account for avoidance of daycare owing to the allergic status.

Specific infections that are acquired in childhood have been queried as causes of food allergy. *H. pylori* infection, the prevalence of which has decreased contemporaneously with the perceived increase in food allergy, has been implicated as a protector against food allergy. *H. pylori*

seropositivity rates explained 32% of the difference between Finland and a geographically similar location in Russia, where infection was inversely related to atopy.[91] A study conducted in the UK found that *H. pylori* infection was associated with a reduced risk of asthma, eczema, or allergic rhinitis, but no statistically significant association was found with them individually,[92] highlighting the need for sufficient sample size within similar studies. To consider whether rotavirus infection may contribute to the development of allergy, Firer et al[93] examined antirotavirus antibody titers in children with cow's milk allergy. A higher proportion of non-IgE-mediated cow's milk allergy cases had evidence of previous infection (76%) compared with IgE-mediated milk allergy (33%, $P = 0.01$). The KOALA study found that there was no association between rotavirus and norovirus seropositivity and eczema or atopy in the first 2 years of life.[94]

Surprisingly given the presumed teleologic development of IgE immune mechanisms for the control of helminthic infections until recently few investigators have examined whether decreased helminthic infestation in westernized countries can be linked to the rise in food allergy[95] although there is an evolving interest in this area as a form of therapy as for inflammatory bowel disease.[96]

## Dietary Influences and Introduction of Food Allergens

The initial timing and dosage of dietary antigens has a profound effect on the change to bowel flora around the time of solid introduction.[97] Exclusive breast feeding seems to have a protective effect on the early development of asthma and atopic dermatitis up to 2 years of age, but the evidence for prevention of food allergies is less clear. The delayed introduction of solids until after 4 months is believed to partially protect infants from developing food allergies, but this has recently been questioned.[65] If exclusive breast feeding is not possible, a hydrolyzed formula is recommended for the first 4 months of life in infants at high risk of food allergy (ie, those with an atopic first-degree relative).[98] Currently there is no evidence for the protective role of maternal elimination diets during pregnancy.[99]

Although all authorities agree that breast milk is the food of choice for infants, the evidence that it prevents allergic outcomes is contradictory, with different studies showing, protection, no effect, and even increased risk.[66,100–110] This may be due to variations in breast milk composition or differences in maternal diet [111–115] but no studies have shown long-term benefits with regard to allergic outcomes. These conclusions also apply to the effect on the prevention of food allergy in particular. Given the current recommendations in many countries to delay the introduction of all complementary foods until 6 months and for much longer delays for specific allergenic foods, it is surprising that the evidence of the effects of delaying the introduction of allergenic foods into the infant diet is extremely limited.

Infant feeding data collected as part of birth cohort studies have been analyzed to investigate the relationship between solid food introduction and the later development of atopy.[116–119] No study found any benefit on allergic outcome by delaying the introduction of solids and 2 found an association between the delayed introduction of milk[116] and egg[117,119] and increased incidence of eczema and atopic sensitization. More recently it has been suggested that children exposed to cereal grains before 6 months of age (as opposed to after 6 mo of age) are protected from the development of wheat-specific IgE.[120] However, all studies collected feeding data retrospectively which makes the findings vulnerable to both recall bias and reverse causality. Nevertheless, these studies have raised the possibility that delaying the introduction of foods into an infant's diet (particularly of allergenic foods) is not beneficial.

## The Role of Genetic Predisposition

Food allergy development is highly likely to be influenced by both genetic and environmental factors. The significant role that genetics plays in these disorders is reflected in a 64.3% concordance rate of peanut allergy between child monozygotic twins compared with 6.8% ($P < 0.0001$) for dizygotic twins.[121] The heritability of peanut allergy is estimated at 81.6% (95% CI 41.6%-99.7%) and found to range from 0.15 to 0.35 for other specific foods in a separate study.[122] The heritability of non-IgE food allergy is not known. Celiac disease, a specific example of food-triggered enteropathy, has shown a very high concordance rate for a multifactorial disease: 75% pairwise concordance (95% CI 62.0%-94.0%) was found among monozygotic twins compared with 11% concordance (95% CI 9.9%-23.0%) among dizygotic twins.[123]

A number of recent studies have linked null mutations (R501X and 2282del4) in the *filaggrin* (*FLG*) gene with an increased susceptibility to eczema,[124] a condition that commonly occurs in infants with IgE-mediated food allergy. Individuals with 2 null alleles in *FLG* have been shown to be 4 to 7 times more likely to have eczema than those without.[125] The FLG protein seems to play an essential role in epithelial integrity. A severe breakdown in the function of the protein produced can result in ichthyosis vulgaris. The association between eczema and IgE-mediated food allergy has been hypothesized to be mechanistic and it has been postulated that the route of sensitization is through damaged epithelia. Marenholz and colleagues[126] proposed that FLG mutations and sensitization to foods act synergistically to increase a child's risk of asthma. However, it is not known whether defects in FLG may act independently to increase the risk of childhood IgE-mediated food allergy itself.[127]

Genes found to convey an increased risk of IgE-mediated food allergy include certain *IL13* gene variants[128] and *IL10* gene variants.[129] The IL-13 and IL-10 cytokines have been implicated in initiation and control of allergic immune responses, respectively. Genes controlling transforming growth factor-β production, another anti-inflammatory cytokine, were not associated with food allergy. Other genes controlling mediators of the allergic immune response, as well as genes that emerge from studies of atopic diseases, are good candidates for research in to the genetics of food allergy.

A better understanding of the genetic predispositions existing to food allergy will lead to the determination of whether a rise in food allergy is occurring asymmetrically between high and low-risk groups. Researchers found that the increasing incidence in type 1 diabetes was explained by an increased disease incidence among lower risk HLA DR4-X and HLA DR3-X genotypes between 1950 and 2005, whereas the incidence of disease amongst the higher risk HLA DR3-DR4 genotype remained constant,[130] indicating a major role for recent environmental changes.

Such research for immune disorders, including food allergy, may be pivotal in directing research toward plausible modifiable risk factors for disease.

## CONCLUSIONS

The rise in food allergy is likely to be linked to factors associated with the modern lifestyle. Further investigation into why some children develop IgE-mediated food allergies and others develop non-IgE mediated food allergy is likely to shed further light on mechanisms of failure of oral immune tolerance in the first year of life. Gastroenterologists are likely to play a central role in understanding mechanisms of non-IgE-mediated food allergies as well as further elucidation of early determinants of health and disease.

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