

New Concepts in Food Allergy The Pediatric Gastroenterologist's View

Neal S. LeLeiko, MD, PhD^{a,b,*}, Carolina S. Cerezo, MD^{a,b},
Jason M. Shapiro, MD^{a,b}

^aThe Alpert School of Medicine at Brown University, Providence, RI 02903, USA; ^bDivision of Pediatric Gastroenterology, Hasbro Children's Hospital/The Rhode Island Hospital, 593 Eddy Street, Providence, RI 02903, USA

Keywords

- Gastrointestinal food allergy • Systems medicine • Network analyses
- Personalized medicine • Precision medicine • Randomized controlled trial

Key points

- There are no universally applicable guidelines for optimal introduction of potentially allergenic foods.
- Randomized controlled trials eliminate many biases but are generally not adequate for development of universal feeding guidelines.
- Practitioners should increase their awareness of eosinophilic esophagitis and several non-immunoglobulin E-mediated gastrointestinal food allergy syndromes because they are being increasingly encountered in practice.
- In the future, guideline-based allergy recommendations may be replaced by individual recommendations based on precision medicine approaches.
- Currently, guidelines need to be very carefully applied to those individuals for whom specific, nonbiased data exist.

INTRODUCTION

The subject of food allergy inspires a great deal of attention from the general population as well as from the physicians who care for patients and families in which food allergy is thought to be an important health concern. The

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*Corresponding author. Division of Pediatric Gastroenterology, Hasbro Children's Hospital/The Rhode Island Hospital, 593 Eddy Street, Providence, RI 02903. *E-mail addresses:* nleleiko@gmail.com; neal_leleiko@brown.edu

primary pediatric care provider is frequently faced with questions regarding primary prevention of food allergy. Feeding concerns as well as gastrointestinal illness, possibly associated with food allergy, generate further questions that are expressed to nonallergist pediatric subspecialists, such as gastroenterologists. With regard to the prevention and treatment of food allergy, this report highlights some of the strengths and limitations of current guideline-based approaches, updates what is known about eosinophilic esophagitis (EoE) and the non-immunoglobulin E (IgE)-mediated gastrointestinal food allergies, and reviews the new concept of a precision approach to food allergy. The authors emphasize the need for this new approach to be developed because they think that when it is developed it will finally enable the legitimate questions of concerned parents to be satisfactorily addressed.

A food allergy is defined according to the National Institute of Allergy and Infectious Disease's expert panel as "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food." [1] Evidence suggests that the prevalence of food allergy is increasing, with reliable estimates of the number of children with food allergy as high as 8% [2]. Food allergy has been a concern for a great many years. Although there are some references that questionably relate food allergy to events in antiquity [3–5], the first scientific report of food allergy seems to have occurred in the early twentieth century [6].

Since then the available information on food allergy has been voluminous. A recent Google search for *infant food allergy* revealed 2,430,000 hits. A similar search on PubMed revealed more than 1800 hits. Even searching for *dog food allergy* revealed 1,990,000 Google hits and 348 PubMed hits. The amount of information available for the public and for health care professionals is overwhelming, but the quality of that information is inconsistent. There is no doubt that significant advances in our understanding of food allergy have occurred over the last century; but we have persisting misunderstandings of various aspects of even common allergy-related issues. For example, many people, including physicians, mistakenly equate *food allergy* with IgE-mediated anaphylactic reactions. Although this is generally the case for peanut and shellfish allergies, the other food allergy processes that the authors discuss are generally considered to be non-IgE-mediated gastrointestinal food allergies (non-IgE-GI-FAs). Although skin prick tests are used for IgE-mediated allergies, they are not useful for the non-IgE-GI-FAs.

Much of the reported research has been observational and prone to excessive bias. There are a few recent high-quality, randomized controlled trials (RCTs) that test a specific intervention and deserve our attention [7–9]. Even these, our best studies, are subject to incorrect interpretation or inappropriate generalizations based on the results.

The tremendous complexity of the pathophysiology of disease in general and especially food allergy has, at least until recently, exceeded the capacity of our available investigative techniques. Even within the context of our

best understanding, outcomes of treatment are often disappointing and sometimes unexpected. There is, therefore, a strong impetus for us to develop and explore novel strategies of research in order to advance clinical practice.

The continuing development and perfection of high-throughput molecular techniques have revolutionized the focus of laboratory-based biomedical research. The large data sets generated from the study of various biological pathways (for example, genome, epigenome, metabolome, microbiome, virome, and so forth) facilitate in-depth analyses that will undoubtedly expand our understanding of these complex immunologic processes. Novel high-throughput techniques and computational analytical techniques allow extremely large amounts of data to be simultaneously measured and analyzed in different conditions over time.

Systems medicine [10,11] is based on combining and analyzing these large data sets. For the authors' purposes, they reference systems medicine when they refer to combining molecular biological findings with clinical metadata from well-characterized patient populations using modern computational methods to determine relevant relationships. An important tool in systems medicine is network analyses. Using techniques often borrowed from other disciplines, ranging from the social sciences to physics, network analyses allow the manipulation, visualization, and the interpretation of the significance of these huge data sets. The networks are, by nature, extremely information rich and enable the harvesting of the huge amount of data available to answer specific clinically relevant questions.

A discussion of the fundamental concepts of network analyses is beyond the scope of this presentation. It is, however, useful to understand that networks are information-rich representations, which assist in the analyses of large data-sets obtained from high-throughput experiments.

The systems approach is needed to clarify the mechanisms by which allergy afflicts humans. Results obtained from our best studies, including RCTs, may eventually be validated and expanded and, it is hoped, unanswered questions resolved through the application of the systems approach. Until then it is important to understand the strengths and limitations of the currently available data.

Although evidence-based, standard-of-care recommendations are needed, there are currently no universally accepted feeding guidelines that can be reliably applied to every infant or child. For example, older concepts of immunology have led to the acceptance of early antigen avoidance as a strategy for primary prevention of food allergy. The resulting guidelines [12] not only failed to prevent food allergy but also, we now realize, actually increase the risk of developing allergy.

Important new studies are having and will have a major impact on current thinking about primary allergy prevention. An examination of the methods and the findings of already published studies should help to provide the basis for critically interpreting their limitations. Also, by looking at some of the methods

and limitations of these studies [7–9] we will be in a better position to identify the gaps to be addressed.

QUESTIONS TO BE ADDRESSED

The authors initially focus on infant feeding and primary food allergy prevention. The results from 3 important recent studies, Enquiring About Tolerance (EAT) [7], Learning Early About Peanut Allergy (LEAP) [8], and Persistence of Oral Tolerance to Peanut study (LEAP-On), [9] are discussed along with their limitations. These studies have attempted to answer the following questions:

Question 1: What is the correct timing for the introduction of potential allergens in breastfeeding infants? [7]

Question 2: What is the correct timing for introducing peanut protein into a regular infant diet? [8]

Question 3: What is the duration of some of the observed outcomes? [9]

In recent years, we have seen a huge increase in the number of children being diagnosed with EoE. The focus of much attention is on answering the following question:

Question 4: What is the place of dietary therapy in the treatment of EoE?

The non-IgE-GI-FAs [13] seem to have been recently rediscovered. The authors review some of the latest concepts in our understanding of the non-IgE-GI-FAs disorders. Included in this disease category are food protein–induced allergic proctocolitis (FPIAP), food protein–induced enterocolitis syndrome (FPIES), and food-induced enteropathy (FPE) and celiac disease (CD). As with the other subjects discussed, our concepts for Non-IgE-GI-FAs (non IgE mediated Gastrointestinal Food Allergies) are undergoing active revision.

The authors' discussion of the new concepts relevant to our understanding of non-IgE-GI-FAs (including CD) focuses on the following questions:

Question 5a: What is FPIAP and what are the new concepts relevant to our understanding of FPIAP?

Question 5b: What is FPIES and what are the new concepts relevant to our understanding of FPIES?

Question 5c: What is FPE and what are the new concepts relevant to our understanding of FPE?

Question 5d: What are the new concepts relevant to our understanding of CD; more specifically, what is the impact of gluten intake on the development of CD [14,15]?

The authors conclude with an extension of their introduction on systems medicine. The focus of the authors' summary is a discussion of how new concepts of personalized nutrition might impact our understanding of nutrition in general and food allergy in particular. The authors' final question is the following:

Question 6: What is personalized nutrition and how might this new approach alter our understanding of food allergy?

QUESTIONS

Question 1: What is the correct timing for the introduction of potential allergens in breastfeeding infants?

One of the most frequent concerns expressed regarding feeding breastfed infants is the following: When is the optimal time to introduce potentially allergenic foods? Perkin and colleagues [7] performed an RCT testing a specific intervention, the early introduction of potentially allergenic foods.

Their study was an RCT conducted between November 2, 2009 and July 30, 2012 at a single center in the United Kingdom. The investigators sought to answer whether the introduction of potential allergenic foods in well breastfed infants at 3 months was protective of the development of allergy when compared with infants who did not receive the allergens until 6 months. They named their study the EAT trial. The allergens tested were peanut, egg, cow's milk, sesame, whitefish, and wheat.

The investigators recruited more than 1300 three-month-old exclusively breastfed infants (average age 3.4 months). The infants were randomly assigned to one of 2 groups. One group, the early intervention group (EIG) was to receive predetermined quantities of allergenic food proteins beginning at 3 months. The other group, or the standard introduction group (SIG), was to be exclusively breastfed for the first 6 months of their lives and then allowed the antigenic foods at the discretion of the parents.

At baseline the EIG infants received allergen skin-prick tests (SPTs). The SIG was not skin tested to avoid undue influence regarding the random introduction of potentially allergenic foods. The EIG received cow's milk, as yogurt first, then in a random order peanut, boiled chicken, egg, sesame, whitefish, and finally wheat.

If an infant in the EIG had a positive wheal on any of the SPTs, the parents were told to avoid that protein but to give each of the other proteins that the skin-test negative infants were receiving.

All families completed online questionnaires each month until 12 months of age and then every 3 months until the infants reached 3 years of age. The questionnaire examined intakes of the potentially allergenic foods. Parents in the EIG kept a weekly diary of the total quantities of the 6 foods consumed.

The complexity of the study called into question the parents' ability to adhere to the details of the protocol. As a result, a post hoc per protocol analyses based on adherence to the dietary interventions was performed. The other analyses were intention to treat, which assumed perfect adherence.

The design was demanding. At 3 months of age, dust was collected from the participants' bed area for measurement of peanut-protein levels. This measurement would verify the peanut-free environment before the introduction of the allergens.[16] Peanut-protein levels in the dust were also collected at 1 year as an independent measure of adherence to the dietary intervention.

Total clinic assessments were scheduled for 1 and 3 years of age, and unscheduled clinic visits were reviewed for allergy-related complaints.

The primary outcome of the study was the development of challenge-proven food allergy to one or more of the 6 studied allergic foods between 1 year and 3 years of age.

At 3 years, 94% of the families were available for analyses. A positive diagnoses of food allergy was based (almost entirely) on double-blind placebo-controlled food challenges.

Positive outcomes were associated with eczema at enrollment, nonwhite race, and having siblings.

The group assigned to receive the allergenic foods early, at 3 months, had 5.6% of their infants develop food allergy, whereas 7.1% of those assigned to the SIG developed allergy. There was no statistically significant difference in the two groups, but this analysis assumed perfect adherence. When assessments of adherence were incorporated in the post hoc per protocol analyses, the results became statistically significant. Although 7.3% of the SIG developed allergy, only 2.4% of the EIG developed an allergy to one or more foods, peanut and egg. There were no cases of peanut allergy among 310 participants evaluated in the EIG versus 13 cases among the 525 (2.5%) who received the standard dietary regimen. There was also a significant difference for egg: 1.4% versus 5.5%.

Participants, whereby adherence removed them from the EIG, developed allergy as if they were in the SIG.

The data as presented are widely interpreted to show that in breastfeeding infants, it is possible to prevent food allergy by the early introduction of multiple allergenic foods. The data certainly are consistent with this view, but the broad application of this interpretation requires some caution. It is noted that there was an issue of adherence in the EIG and therefore the amounts of allergenic protein are very difficult to know with certainty. Given these limitations, the practical application of the results needs to be viewed in context. It seems clear that delaying introduction of the allergenic foods in otherwise healthy breastfeeding infants is *in general* not an optimal strategy. The guidelines that advise delay cannot be defended. That is a very important contribution to infant feeding practices. The study does not provide unequivocal rules of the correct introduction of allergens, however. One may suspect that there might be significant variability from infant to infant. Also, at what point in time the introduction of allergenic foods becomes irrelevant or adverse is unknown. It is also possible (although speculative) that the amount of antigen presented to each infant might affect the results. It is hoped that the variety of these unanswered questions will one day be answered by using complex analyses of a large cohort of patients whereby the knowable unknowns are adequately evaluated and where a valid multidimensional systems analyses can be carried out.

Question 2: What is the correct timing for introduction of peanut into the regular infant diet?

In February 2015, the *New England Journal of Medicine* reported on the landmark LEAP study [8]. LEAP [8] was the result of concerns about preventing the

development of severe peanut allergy. LEAP, conducted at a single site in the United Kingdom, was a randomized open-label controlled trial. The primary outcome of this trial was the number of infants who developed peanut allergy at 5 years of age after either avoiding peanut or being exposed early in their lives to peanut antigen.

Participants were enrolled between 4 and 11 months of age. They were all considered to be at high risk for developing peanut allergy [17] based on a history of either eczema and/or egg allergy. Well infants with no known risk of developing peanut allergy were totally excluded from this study.

All infants received an SPT for peanut allergy. If an infant's SPT was greater than 4 mm, the infant was also excluded from the study. Therefore, both those without any known risk of allergy, that is, completely healthy normal infants, and those with evidence of the most severe allergy as defined by a SPT greater than 4 mm were excluded. The other infants were divided into the 2 study cohorts by having a skin wheal that measured between 1 and 4 mm or no measureable wheal at all. Infants in both cohorts were then randomly assigned to either the peanut-avoidance group or the peanut-exposed group (Fig. 1, modified from Du Toit and colleagues [8]).

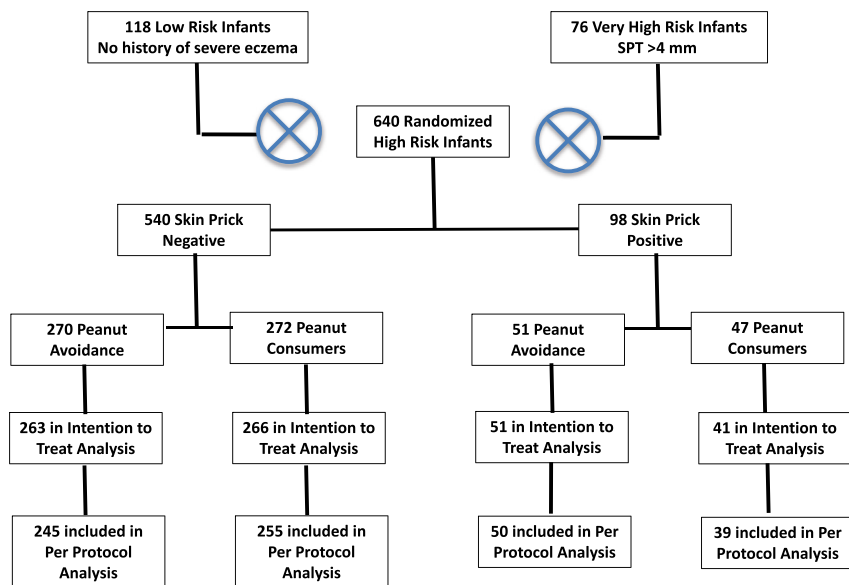


Fig. 1. The infant groups studied in the LEAP trial. The diagram provides an overview of the groups studied as well as the numbers of children who were excluded because they either had no history of severe eczema or no positive finding of a SPT greater than 4 mm. (Data from Du Toit G, Roberts G, Sayre PH. et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372:803–13.)

Each infant in the peanut-exposed group was to receive a minimum of 6 g of peanut protein per week, which had to be divided over a minimum of 3 meals. The protein source was a food with a well-characterized peanut protein content. The primary outcome was to determine if early introduction of peanut to these infants reduced later development of peanut allergy.

Validated food questionnaires [18] and measures of environmental dust [16] were used to assess adherence.

Members of both skin-prick cohorts were randomly assigned to either consume peanut or not. Those assigned to eat peanut-containing foods were given an oral peanut challenge; if they reacted, they were told to avoid peanuts (but included in the intention-to-treat analysis).

In total, 640 participants were randomized (see Fig. 1), 542 who had a negative SPT and 98 who were positive. Half the participants in each group were assigned to peanut avoidance and half to peanut consumption. Participants were evaluated clinically at intake and at 12, 30, and 60 months of age and underwent repeat SPTs and tested for peanut-specific IgE, IgG, and IgG4 antibodies. At 60 months, infants underwent their final SPTs as well as an oral food challenge.

Outcomes were analyzed for both intention to treat and per protocol using a 2-tailed chi-square test.

The negative skin-prick group contained 530 participants who were evaluated for peanut allergy. Approximately 14% of the peanut-avoidance group but only 2% of the peanut-consuming group was positive for peanut allergy. The results suggested a statistically significant 86% relative reduction in the prevalence of peanut allergy. Similarly, in the positive skin-prick group, among the 98 participants, there was a statistically significant 70% relative reduction in the prevalence of peanut allergy favoring those who consumed peanut.

Secondary outcomes were skin-prick testing results and select immunoglobulin levels. In the peanut-avoidance group there was an increase in skin wheal size, but in the peanut-consumption group there were higher levels of peanut-specific IgG and IgG4. The investigators considered an elevated peanut-specific IgE to be associated with an increased risk of allergy and an elevated peanut-specific IgG4 to be associated with a decreased risk. Both groups showed increases in peanut-specific IgE. Although the peanut-avoidance group was more likely to achieve peanut-specific IgE, the calculated ratio of IgG4 to IgE was higher in the consumption group. Furthermore, it was less than the mean in almost all the peanut-allergic participants.

The outcomes were consistent between the intention-to-treat and per-protocol groups. The authors concluded:

Our findings showed that early, sustained consumption of peanut products was associated with a substantial and significant decrease in the development of peanut allergy in "high-risk infants" [but recall that the very "high-risk" infants with skin-prick wheals ≥ 5 mm were excluded from the study].

Conversely, peanut avoidance was associated with a greater frequency of clinical peanut allergy than was peanut consumption, which raises questions about the usefulness of deliberate avoidance of peanuts as a strategy to prevent allergy.[8]

This study is an extremely valuable study that alters our thinking on food allergy. Because of an accumulation of observational studies on the development of allergy, the American Academy of Pediatrics (AAP) recommended [12] that infants not be fed peanuts until they were at least 3 years of age. It was thought that this would lessen the risk of developing peanut allergy. Subsequently, increasing evidence [19–21] associated with other foods suggested a benefit from early introduction of potentially allergenic foods. This evidence led to this landmark LEAP study [8], which confirms the AAP's retraction of its original guideline [22]. LEAP confirms that withholding peanut is a mistake. The groups studied, however, were medium risk, that is, not the very-high-risk infants (those with skin-prick wheals ≥ 5 mm) and not the low-risk healthy infants. Even in those tested, it is not clear how much peanut protein needs to be ingested and for how long it needs be ingested.

Expert opinion suggests “that for any infant between 4 months and 8 months of age believed to be at risk for peanut allergy should undergo skin-prick testing for peanut.”[23] It is further recommended that if the test is negative, 2 g of peanut protein be fed at least twice a week for at least 3 years and if there is a 0- to 4-mm wheal, an oral food challenge should be administered.

These recommendations are reasonable, but what they really allude to is the inadequacy of a single all-encompassing guideline for everyone. They suggest that in an ideal world we would have more information at our grasp to predict who would and would not benefit from any particular approach.

Question 3: What is the duration of the observed outcome benefit of early introduction of peanut?

Du Toit and colleagues [8] have provided very important information but were not able in the LEAP study to address the question as to whether those infants and children who benefitted from the early introduction of peanut protein could sustain that protection if they experienced a prolonged period without peanut consumption. Assessing the persistence of protection from early peanut consumption became the focus of their next study [9], LEAP-On. LEAP-On was a 1-year extension of the LEAP study.

All of the children who were in the intention-to-treat group in LEAP were available to continue with a 1-year extension during which they were to forego any peanut intake. The objective of LEAP-On was to determine if allergy avoidance for the year following participation in LEAP (aged 60–72 months) resulted in a loss of the protection provided by early peanut antigen ingestion. (It did not.) As with LEAP, adherence was assessed in part by the use of a validated peanut-frequency questionnaire [18] as well as by measuring peanut protein levels in dust collected from the participant's beds.

The percentage of infants who developed peanut allergy at 72 months of age was the primary outcome measure. Oral peanut challenge at 72 months of age was used to determine the presence of allergy. Immune markers, including peanut-specific IgE and IgG4 levels as well as specific IgE responses to the peanut protein Ara h2, were also measured. The rates of peanut allergy at 6 years were compared between the original avoidance and peanut-consumption groups.

Peanut allergy was confirmed in 18.6% of the participants in the original avoidance group versus 4.8% of those in the peanut-consumption group. It was also noted that 3 new cases of allergy developed in each group. Also 4 participants in the initial avoidance group who were allergic at 60 months of age were peanut tolerant at 72 months of age.

The investigators concluded: "...the early introduction of peanut induced unresponsiveness to peanut that persisted after 12 months of avoidance...It remains to be seen whether the effects of peanut consumption in early life are maintained if peanuts are consumed ad libitum over the course of many years." [9]

The study could not provide insight into either the amount or duration of peanut intake that is necessary to induce tolerance to peanut. It was also unable to identify biomarkers for the later acquisition of peanut allergy.

In summary, infants and children who consumed peanuts for 4 to 5 years early in life experienced "stable unresponsiveness" to peanut antigen that persisted after 12 months of peanut restriction. For those children who were at significant allergic risk to peanuts, who develop oral tolerance during their first 5 years, LEAP-On shows that tolerance persists for most children even after avoiding peanuts for 12 months. It remains unknown, however, whether the effects of peanut consumption early in life are maintained through childhood and adulthood.

LEAP and LEAP-On are very important studies that provide some general guidance. They do not, however, inform us about the optimal approach to adopt for all infants. To participate in the original LEAP study, atopic babies were divided by their peanut SPT: no measurable wheal after testing versus a wheal measuring 1 to 4 mm in diameter. As mentioned earlier, the results of these studies are not generalizable to low-atopic-risk infants or to those who are highly allergic (as manifested by the more positive SPT) because both of these groups were excluded from these studies. It remains our task to appreciate the strengths and importance of the available data but also to understand their limitations. At this time, for many of our patients, an informed, moderate, middle-of-the-road approach that seems most likely to do no harm seems the best approach.

Question 4: What is the place of dietary therapy in the treatment of eosinophilic esophagitis?

Consensus reports define EoE as a "chronic, immune/antigen mediated, esophageal disease characterized clinically by symptoms related to esophageal

dysfunction and histologically by eosinophil predominant inflammation.”[24] The immunopathogenesis is likely attributed to a combination of IgE and non-IgE-mediated mechanisms. There exists no single test to positively establish the diagnosis of EoE. Clinicians generally rely on a combination of frequently observed symptoms as well as biopsy results. Eosinophilic infiltration of the esophagus alone is not enough to establish the diagnosis. The presence of greater than 15 eosinophils per high-power microscopic field that cannot be explained by other conditions, such as gastroesophageal reflux, is considered consistent with EoE. Box 1 lists causes of esophageal eosinophilia that should be excluded before establishing the diagnosis of EoE.

Over the past 10 to 20 years, EoE has become well known to pediatric gastroenterologists. EoE seems to have a significant male preponderance [25]; although a positive family history of allergic disease may be associated with the diagnosis, studies suggest a stronger environmental versus genetic role. It is estimated to have a prevalence in the United States of 0.5 to 1.0 case per 1000 children and adults [25].

EoE is a leading cause of food impaction and dysphagia in older children and adolescents [26] and is a frequent cause of referral for feeding problems in younger children [27].

Some have described what is referred to as proton pump inhibitor (PPI)-responsive esophageal eosinophilia [28]. These patients' esophageal eosinophilia seems to clinically and histologically remit with 8 weeks of therapy

Box 1: Potential causes of esophageal eosinophilia

EoE

Gastroesophageal reflux disease

Proton pump responsive esophageal eosinophilia

Eosinophilic gastroenteritis

Drug allergy

Achalasia

Infections

Immune-related diseases

CD

Immunodeficiencies

Crohn's disease

Allergic vasculitis

Parasitic infection

Eosinophilic leiomyomatosis

Graft-versus-host disease

Systemic eosinophilia (for any reason)

with a high-dose PPI. Various regimens, many involving the continuation of administration of a PPI, have been proposed for maintenance of initial remission. They have been summarized by the European Society for Pediatric Gastroenterology Hepatology and Nutrition's Eosinophilic Esophagitis Working Group and the Gastroenterology Committee [29]. Proposed mechanisms of action for symptom remission include the activation of gastroesophageal reflux disease-like symptoms by the eosinophils [30,31]; a direct pharmacologic effect on inflammation suppression by the PPI [32]; inhibition of expression of adhesion molecules, neutrophil activation, and production of proinflammatory cytokines [33]; blockade of STAT6 binding; and inhibition of interleukin 4-stimulated exotoxin-3 expression.[34] Treatment outcome reports vary widely.

There are some prospective data from healthy adults indicating that PPI therapy increases the risk of sensitization to dietary antigens and even manifestation of food allergy [35]. Long-term studies on the impact on children and young adults of prolonged therapy with PPIs are mixed, although not necessarily alarming [36–38].

The other pharmacologic agents used to treat EoE are topical corticosteroids (CS), such as fluticasone and budesonide. Studies have shown the effectiveness of CS for treating EoE [39–41]; but CS are not approved by the Food and Drug Administration for use in EoE, and these agents are prescribed for off-label use. Studies of newer agents [41] are promising, but safety must remain a concern pending larger and long-term studies.

Although CS remain a popular therapeutic option, their beneficial effect on symptoms can lead to their prolonged use and eventually to associated steroid-related complications, such as adrenal suppression [42–44].

The appreciation of the role of food allergy has led to a strong advocacy for treatment based on antigen avoidance, that is, dietary therapy. Dietary therapy induces a clinical response associated with histologic remission in pediatric and adult patients [45–47]. The other obvious advantage is that the side effects associated with medications are avoided. The adequacy of the diet is best assured by consultation with a registered dietician.

Dietary approaches include using [1] an amino acid-based formula that is nutritionally complete but nonallergenic [2]; a targeted elimination diet (which is based on the results of allergy testing, usually skin patch and skin-prick testing as well as serum IgE levels); and finally [3] an empirically based elimination diet. Empirically based elimination diets and their reported efficacy [47] include the 6-food elimination diet (reported efficacy of 72.1%), the 4-food elimination diet (reported efficacy of 68.2%), and the targeted diet, based on skin testing (reported efficacy of 45.2%). Total elemental diets seem to be in excess of 90% efficacy [47]. Based on the restrictiveness and practicality of these approaches, many gastroenterologists are opting to treat with either the 6- or 4-food elimination diets.

In general, the antigens avoided are the most frequently offending foods, that is, milk, wheat, eggs, soy, seafood (shellfish and fish), and nuts (peanuts and tree nuts). Once a patient is under control, the identification of the offending

foods is performed based on selective reintroduction. This process can be laborious and of course requires substantial commitment on the part of patients and families. Adherence, as the authors reviewed in their discussion of infant feeding in the course of RCTs can be extremely problematic. It is possible if not likely that EoE should not be considered as a single diagnosis but rather is the histologically observed lesion that results from variation in pathologic mechanisms in different people. Precise diagnostic and treatment plans are obviously a priority for effectively managing EoE.

Question 5: What are the non-immunoglobulin E-mediated gastrointestinal food allergies?

There is relatively new interest in the non-IgE-mediated gastrointestinal food allergy syndromes. Although these conditions have likely been around for a long time, they are being increasingly recognized and diagnosed by practitioners. CD is the best known and most common, occurring in approximately 1% of the Caucasian population [48]. With regard to the nonceliac, non-IgE-GI-FAs, an examination of the literature suggests that the definitions and the pathophysiology of these syndromes is still undergoing revision and refinement. Patients with these syndromes may present to their primary care physicians (PCPs), be referred to a pediatric gastroenterologist for consultation, be referred to allergists (with varying degrees of pediatric expertise), or be admitted to a hospitalist service with acute or chronic medical issues. As a result, the descriptions and definitions of these syndromes, with the exception of CD, are somewhat descriptive; there is overlap with emphasis often based on the specific training and expertise of the investigator or treating physician. With the increased amount of attention [13,49–57] they are receiving it is likely that better categorization will go hand in hand with a better understanding of their pathophysiology.

The non-IgE-GI-FAs include (Table 1)

1. FPIAP
2. FPIES
3. FPE
4. CD

Question 5a: Food protein-induced allergic proctitis

FPIAP (see Table 1) is probably the most frequently encountered of the non-IgE-GI-FAs. The actual incidence is unknown, but there is clearly an impression that it is occurring more frequently in recent years. The typical onset is within the first few weeks of life, but some infants seem to present after the first month with decreasing frequency during the first 6 months. Although typically this is associated with infant formula, it also occurs in breastfed infants. In breastfed infants, mothers are usually counseled to remove milk protein products from their own diet with a generally acceptable (although not universal) rate of response in the affected infants. Alternatively, and especially with formula-fed infants, a protein hydrolysate is substituted for milk protein

Table 1

Comparison of non-immunoglobulin E-mediated gastrointestinal food allergies

	Food Protein Induced Allergic Proctitis FPIAP	Food Protein Induced Enterocolitis Syndrome FPIES	Food Protein Induced Enteropathy FPE	Gluten Sensitive Enteropathy "Celiac Disease"
Incidence	"Infant cow milk colitis" also occurs in breast fed infants ??	Anytime in first year - related to antigen exposure ??	Related to antigen exposure ?? (probably least common)	~ 1%
Age at onset	First days to up to 6 mo	Anytime in first year - related to antigen exposure	Can probably occur at any time (especially after acute enteritis)	Any time after gluten exposure (can present in adults)
Offending foods				
Cow's milk	++++ (Mothers milk?)	++++	++	—
Soy	++++	++++	++	—
Rice	+	++++	++	—
Oats	+	++++	++	—
Wheat	+	++	++	—
Eggs	+	++++	++	—
		Other proteins	++	Gluten
Atopic history	Probably similar to general population	Variable - but frequently present	Variable	
GI symptoms				
Bloody diarrhea	Frankly bloody or blood streaked or only occult blood positivity/mucousy stools	Can be very severe	Emulates any malabsorption syndrome - especially a post-infectious cause	No
Vomiting	No (but unrelated infant spitting up or reflux is not unusual)	Can be very severe	Can be intermittent	Generally no
Diarrhea	++	Severe	Yes - but generally NOT bloody	Yes/no X% with constipation
Systemic symptoms	May be irritable	Can be very severe	Mild to moderate	Chronic
Shock	No	Well know to occur	No	No
Hypoproteinemia	No	Often	Yes - especially over time	If untreated
Edema	No	May be secondary to severe acute hypoalbuminemia prob	With hypoproteinemia	

Chronic symptoms	No	Associated with severity	More prominent than acute symptoms	If untreated
Failure to thrive	Usually no, but can occur if a timely diagnosis is not made	Associated with extent of damage to intestine and difficulty with finding adequate feeding regimen	Over time - especially if sx are not recognized and evaluated	If untreated
Anemia	Over time if bleeding is prolonged	Relative to severity of other symptoms	Secondary to iron deficiency and malabsorption	May present with iron deficiency
Allergy Eval				
Skin Prick Test	Neg	+’ve in less than 50%	Unknown	Neg
IgE related to foods	Neg	Neg	Unknown	Neg
Total IgE	Nml (can be elevated)	Nml (can be elevated)	Unknown	Neg
Small Intestinal bx	Nml	Patchy to confluent damage	Expect to see villous damage	Villous atrophy
Colon bx findings	Focal colitis may have eosinophilic infiltration of rectal mucosa - if biopsied	Inflammation +/- ulceration	Infrequent	Minimal to none
Treatment	Allergen avoidance (hydrolysate formulas or up to 10% may need amino acid formula)	Allergen avoidance (hydrolysate formulas or up to 10% may need amino acid formula)	Food elimination, rechallenge at 1-2 y	Gluten - free diet
Natural history	Acute symptoms resolve over two weeks if offending allergen is removed. Allergy generally resolves by 12 mo	Subject to misdiagnosis because of non-specific findings and prolonged course which is variable in different populations, but can out grow anytime from months up to 5 y	Resolves over time, but can be 2-3 y of longer	On gluten-free diet symptoms respond over a variable amount of time - days to months
Diagnosis	Based on elimination of offending allergen (usually cow’s milk protein) can offer milk protein challenge at one year	Based on removal of offending agent. Can confirm only with oral food challenge - which carries it own risk.	History, small bowel biopsy, and food challenge	Various antibodies may be suggestive but typical small bowel biopsy is definitive

Abbreviation: GI, gastrointestinal.

Data from Nowak-Węgrzyn A. Food protein-induced enterocolitis syndrome and allergic proctocolitis [review]. Allergy Asthma Proc 2015;36(3):172–84.

products. An adequate response would include no worsening and clear improvement within 2 weeks. If there is an inadequate response, an amino acid–based formula is required. Many infants may have been switched by their PCP to a soy-protein–based formula, and the rate of success of this approach is unknown. Clearly, many infants do not respond or develop *de novo* allergy to soy, as they are typically the ones referred for subspecialty evaluation. The condition is considered to resolve over months to 1 year. Generally, the longer the symptoms persist, the more likely there are other associated allergic conditions. The presence of eczema or other allergic signs also suggests a more complex cause and course.

Question 5b: Food protein–induced enterocolitis syndrome

FPIES (see Table 1) is the most notorious of the non-IgE-related food allergy syndromes. Although a chronic form is described, the most threatening form is the acute-onset form. Typically, the infant becomes ill within 1 to 4 hours of ingestion of the offending allergen. The ill infant may exhibit profuse vomiting and/or diarrhea, dehydration, and shock. The chronic form has similar, although considerably less dramatic symptoms over time with prominent hypoalbuminemia, malabsorption, and failure to thrive. The acute form is more likely to be misdiagnosed as a severe infection, other systemic disease, or surgical abdomen. In newborns, it may even be misdiagnosed as necrotizing enterocolitis [54]. Cow's milk and soy protein seems to be the most common offending antigen in infants, although similar syndromes have been attributed to soy, fish, wheat, and egg in older children.

Question 5c: Food protein–induced enteropathy

Food protein–induced enteropathy (see Table 1) is probably the least common of the 3 entities. It usually is a disease of infancy. Although it may present with acute symptoms such as vomiting and diarrhea, it is probably more likely to present as chronic malabsorption with failure to thrive. The differential diagnosis includes pancreatic insufficiency [that is, cystic fibrosis] and celiac disease. It may appear as a prolonged enteritis following a real or apparent acute enteritis picture. Although the syndrome is associated with the same allergens as the other forms of non-IgE-mediated gastrointestinal food allergy, the question of its possible occurrence in breastfed infants is not resolved.

Question 5d: Celiac disease

The relative contribution of [1] the age at which an individual first encounters gluten [2], the amount of gluten in the diet, and [3] the genetic predisposition to CD are unknown. HLA haplotypes DR3-DQ2 and DR4-DQ8 are necessary for CD, and approximately half of the Caucasian population possesses at least one of these haplotypes and virtually everyone consumes gluten. Given these facts, it may be considered surprising that only about 1% of the various Western Caucasian populations are affected by CD. This finding raises the question of other factors, including the environment. Liu and colleagues [58] studied the risk of pediatric CD according to HLA haplotype and country of birth. They

studied 6403 children who were participating in The Environmental Determinants of Diabetes in the Young (TEDDY) study. TEDDY [58] is following more than 8000 newborns at high genetic risk of developing type 1 diabetes until they are 15 years old to identify environmental triggers of disease. Participants in the TEDDY study were from the United States, Finland, Germany, and Sweden. The investigators applied a standard protocol to try to minimize the differences that might influence the impact of the environment. The participants had the appropriate haplotypes and were studied prospectively from birth until the development of positive CD autoimmunity or of CD. CD autoimmunity was defined as seroconversion to positive antibodies to tissue transglutaminase (tTG). The median time of follow-up was 60 months. CD autoimmunity (the primary end point) developed in 786 or 12.0%, and 312 or 4.8% fulfilled the study criteria for the diagnosis of CD (the secondary end point).

Ultimately it was shown that Swedish children had almost twice the risk of developing CD autoimmunity or CD than did children born in the United States. Swedish children were exclusively breastfed for the longest period (median 4 weeks), and children in the United States were exclusively breastfed for the shortest period (median 1 week). Overall breastfeeding was the shortest in the United States (median 30 weeks) and longest in Finland (median 39 weeks). Of note, the Swedish children were introduced to gluten-containing foods at the earliest age. Aronsson and colleagues [59] concluded that the age at which children were introduced to gluten did not explain the increased incidence of CD observed. They believed that future reports would need to examine the importance of variables such as early life infections, other genetic factors, and the environment. To clarify the role that the quantity of dietary gluten might play, Aronsson and colleagues [59] undertook to determine if the amount of gluten in the diet until 2 years of age affects the risk of developing CD. They conducted a 1-to-3 nested, case-control study of 146 cases resulting in 436 case controlled pairs. The pairs were matched for sex, year of birth, and HLA. Screening for antibodies to tTG was routinely performed yearly starting at 2 years of age. Serum samples were collected and frozen every 3 months. Once a tTG antibody study turned positive, the previously frozen samples were tested to determine the time of seroconversion. CD was confirmed by intestinal biopsy. Gluten intake was calculated from 3-day diet diaries collected at 9, 12, 18, and 24 months of age.

Breastfeeding duration and age of introduction of gluten did not differ between cases and controls. However, the amount of gluten consumed before 2 years of age increased the risk of CD by at least 2-fold among the genetically susceptible children. Cases were found to have a larger intake of gluten than controls.

The prospective design of the study enabled the unbiased accumulation of diet information before the development of both tTG seroconversion and biopsy-proven CD.

The significance of the lag period between early gluten ingestion and actual development of CD is of particular interest. The accompanying editorial [15] pointed out that early high gluten intake may only be a marker for later gluten intake or some other phenomenon contributing to development of the disease. The issue cannot be considered resolved.

However, the following question remains: how do these data influence what we recommend to healthy at-risk patients? It would seem that we remain constrained in our recommendations and would need to argue for modest, middle-of-the-road recommendations, in other words a modest intake of gluten in early life. It would seem imprudent to try to eliminate gluten from the infant diet or similarly to advise high-level consumption. The appropriate approach would certainly require individualized counseling with a nutritionist specializing in CD to review family and infant diets. Clarification of the questions posed is not likely until a greater understanding of the mechanisms involved and the individual variations associated with the mechanisms is achieved.

Question 6: Concluding comments

Personalized nutrition and precision medicine?

The observed increase in allergy over the past few decades may be mediated by complex interactions at mucosal surfaces between the immune system and various antigenic triggers. The antigens involved may be foods and/or microbes and may be facilitated by factors that impact mucosal integrity, such as emulsifying agents found in processed foods. At the interface of the environment and immune system is our genetic makeup, including our epigenome. The environmental-genetic interactions may be mediated via epigenetic pathways, including DNA methylation [60]. High-throughput methylation profiling of immune cell subtypes or whole blood may lead to the identification of important biomarkers of allergy [60].

Changes in our environment are implicated in other immune-related diseases, such as inflammatory bowel disease. Yatsunenکو and colleagues [61] have shed light on how the human microbiome develops in the first years of life. The exact role of diet, method of birth delivery, exposure to household pets, and birth order need to be clarified. These factors are among the many factors likely to impact the composition of the individual's microbiome in general and intestinal microbiome in particular. The role of the microbiome in food allergy is beginning to be addressed. Blázquez and Berin [62] have reviewed studies that support a relationship between intestinal dysbiosis and allergy. It is likely that this dysbiosis impacts the innate and adaptive immune systems to potentially trigger sensitization and allergic reaction. This understanding is consistent with animal models in which specific species are associated with specific outcomes related to allergy.

Genetic studies further suggest that patterns of allergy are complex and probably associated with hundreds of genes. Genome-wide association studies related to IgE-mediated allergy have identified peanut allergy-specific loci and evidence of epigenetic influence [63]. The HLA-DQ and HLA-DR gene

regions seem most likely associated with the relevant genetic polymorphisms. Genetic associations alone, however, cannot be considered to have played a major role in the recent increase in allergy occurrence. Changes in our environmental exposures offer a more reasonable explanation for the observed increase in allergic disease, probably in association with genetic predisposition.

To make sense of what is happening it will be necessary to use a systems biology approach. The clinical implications of omics and systems medicine with an emphasis on personalized, precision approaches that move beyond guideline-based medicine are becoming clearer [64–66]. Approaches using systems biology and precision medicine to better understand allergy are underway [67].

We will need to acquire large numbers of well-characterized individuals for whom we have clinical, dietary, metabolic, genetic, epigenetic, microbiomic, and other omics data available. The data will have to be assembled and evaluated along with the more conventional forms of clinical metadata to facilitate disease prediction and therapy (Fig. 2).

The computational task will be formidable and subject to limitations similar to those confronting current analyses in other immune-related diseases, such as Crohn's disease [68]. Other, yet-to-be-identified limitations may also become apparent.

Zeevi and colleagues [69] recently published an example highlighting the importance of a multifactorial approach to complex metabolic questions. Studying patients with diabetes, they noted that despite many written guidelines for

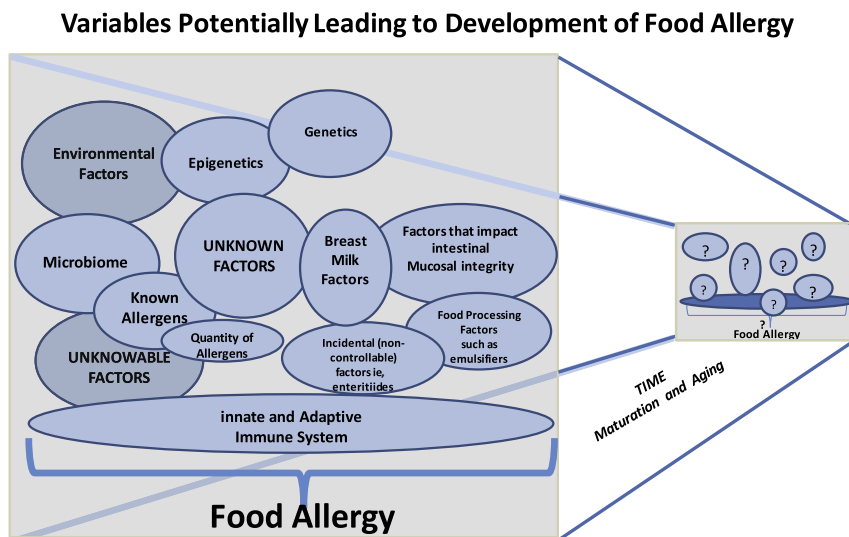


Fig. 2. Potential interplay between known and unknown factors potentially leading to the development of allergy. It is likely that over time the relative importance and interplay of these factors will change.

controlling postprandial glycemic response, in real-life situations the guidelines did not seem to work. The investigators were able to predict an individualized glycemic response using an approach that integrates the gut microbiome (at an age whereby it is likely to be relatively stable) as well as the analyses of blood glucose, dietary contents, and metabolic parameters (as represented by physical activity).

The high throughput and complex computational analyses foretell an era whereby individualized risk assessment or a recommended dietary program is designed to optimize health-related outcomes.

As with food allergy, there have been and remain numerous advisories (for diabetic patients) that seem to be sensible and are widely advocated, yet do not explain discrepancies between expected and real outcomes. Zeevi and colleagues [69] suggest that universal dietary recommendations may be of limited use in predicting postprandial glucose response in patients with diabetes, and the authors suggest similarly that universal dietary recommendations are likely to be of limited use in predicting development and outcomes related to food allergy.

Greer and colleagues [22] writing on behalf of the Committee on Nutrition and the Section on Allergy and Immunology of the American Academy of Pediatrics corrected an earlier policy statement on the use of hypoallergenic infant formulas. That same statement made provisional recommendations for dietary management to avert the development of atopic disease in infants and children. The investigators reviewed conflicting studies and concluded, "it is evident that inadequate study design and/or a paucity of data currently limit the ability to draw firm conclusions about certain aspects of atopy prevention through dietary interventions." [22] They recommend more studies to clarify the correct approach.

The anticipated goal of investing in studies that leverage high-quality clinical and biological data with high-throughput analytical methods and advanced computational methods is to be able to provide person-specific (precision medicine) prescriptions that will eventually render our current guidelines-based approach obsolete.

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