Food Allergy and Complementary Feeding

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Abstract

The relationship between complementary feeding and the development of atopic disease is the source of significant interest and debate in both the scientific and lay communities. A small number of early studies, which had considerable influence on recommended feeding practices, reported protective effects associated with delaying the introduction of commonly allergenic foods such as cow’s milk, egg, and nuts. Despite more conservative recommendations, however, food allergy prevalence has continued to rise. Our understanding of the development of food allergy, its relationship with IgE sensitization and atopic dermatitis, and the relationship of each of these outcomes with the timing of food introduction has evolved considerably. Based on multiple observational studies, and extrapolating from immunotherapy trials and animal models of mucosal immunity, there is mounting evidence that delayed introduction or avoidance of commonly allergenic foods is at best neutral and may be detrimental with regard to atopic outcomes. There is an obvious and critical need for additional high-caliber studies to further evaluate this connection. In the meantime, multiple health considerations, not allergy alone, should be involved in decisions regarding nutritional intake, including common allergenic foods, during the period of transition to the family diet.

Introduction

Complementary feeding refers to the introduction of first foods and the transition from breast milk or infant formula to the adoption of the family diet, usually completed by around 18–24 months of age. This is accompanied by decreased reliance on liquid as a primary source of nutrition.
Atopic diseases have increased rapidly and in correlation with westernized lifestyle, strongly implicating environmental factors. Clinical food allergy, sensitization to foods (positive skin or serum testing), and atopic dermatitis often occur within the first 1–3 years of life. A few foods (milk, egg, wheat, peanut, soy, fish) account for a large percentage of food allergy in young children.

Some influential early studies found evidence that delaying introduction of more allergenic foods was potentially protective against food allergy and/or atopic dermatitis at an early age [1–3]. Based on these findings, both US and European bodies endorsed conservative recommendations or policy statements with respect to the timing of introduction of some foods [4, 5].

Despite these recommendations, the incidence of food allergy and atopic dermatitis has continued to rapidly increase over the past decade – by some assessments even faster than that of other atopic disease (e.g. asthma, allergic rhinitis) [6, 7]. In addition, the preponderance of data now available fail to show clear risk reductions for these outcomes by delaying the introduction of foods [8], and some suggest the opposite: that delayed introduction may enhance risk of food allergy [9–14]. However, the data are still limited and sometimes conflicting, especially given that clinical outcomes, such as food allergy, are often only partially characterized by measuring specific IgE.

In order to relate this literature to the questions most often posed by patients and their families, it may be helpful to separately evaluate what is known about the effects of complementary feeding on clinical outcomes in high- or low-risk infants. Furthermore, this must be achieved with the understanding that there is overlap, but not tight correspondence, between these outcomes (fig. 1). Those outcomes that are of most interest to patients are clinical food allergy (IgE mediated or non-IgE mediated), atopic dermatitis and the course of established allergy. Allergic sensitization (positive skin prick or serum IgE test) is not a clinically relevant outcome per se. When present, it should be rigorously corroborated with the clinical history, ingestion challenges and periodically reassessed. This is especially true early in life.

**Fig. 1.** Model of the overlapping but distinct outcomes discussed.
as the relationships between exposure, sensitization and clinical disease are often very dynamic over time (fig. 2).

As the available data are often insufficient for making recommendations that are truly evidence based, until prospective randomized controlled studies are designed to address those gaps, we must cautiously use the information we can deduce from other contexts including observational studies, immunotherapy trials, and even animal models of mucosal immunity.

**Modifying the Risk of IgE Sensitization**

Allergic sensitization refers to the documentation of allergen-specific IgE, either by in vivo skin prick testing or detection of specific IgE in serum. Two things are important to note about this outcome. First, there can be biologically relevant discrepancy between skin prick testing and in vitro serum testing. Skin testing is an in vivo exposure, and reactivity depends on the presence of allergen-specific IgE with the capacity to induce cross-linking of high-affinity IgE receptors on mast cells armed with allergen-specific IgE — a capacity that is influenced by qualities of the IgE repertoire [15] (e.g. the polyclonality, the individual affinities of those clones, and the specific/total IgE ratio) as well as the intrinsic properties of the patient’s mast cells [16]. Second, regardless of the method of detecting sensitization, only a subset of those who are sensitized will prove to be clinically allergic. For example, while the prevalence of clinical peanut allergy is approximately 0.5–1% [7], a large unselected population-based evaluation of peanut sensitization by skin testing revealed a prevalence of 8.6% [17], suggesting a false positive rate of ~90%. This rate is likely to be lower among younger children who have not
yet become sensitized to potentially cross-reactive airborne allergens [18]; however, in a study of 1,072 children 4–5 years of age, the false positive rate was still ~35% [19].

One of the early studies to address the role of complementary feeding in high-risk infants did find evidence of protection and played a significant role in supporting conservative recommendations of potential allergen exposure [3]. Zeiger et al. [20] conducted a prospective, randomized, interventional study of high-risk children, where either the introduction of common allergens (milk after 1 year, egg after 2 years, peanut after 3 years) was delayed, or standard feeding practices were followed. The intervention also included maternal avoidance of common allergens in the third trimester and while breastfeeding. Families following the conservative schedule had lower rates of sensitization to milk at 24 months of age. However, in a follow-up report at 7 years of age [3], no significant difference in sensitization to any food allergen remained.

A systematic Cochrane review on the optimal duration of exclusive breastfeeding published in 2002, and updated in 2009, did not assess the outcome of food allergen sensitization [8]. However, Zutavern et al. [21] reported the rate of sensitization to foods (egg, milk, peanut, soy, wheat and fish) by serum IgE testing (CAP-FEIA) in a large birth cohort. Feeding was assessed at 6 months. Approximately 1/3 of the children received foods before 4 months of age, while half were exclusively breastfed in the same period. Twelve percent of the analyzed population were sensitized to one or more of those six foods. To take into account reverse causality, analyses were also performed excluding children with rash or allergic symptoms in the first 6 months of life. There was no protective effect of a late introduction of solid foods (>4 or >6 months) or a less diverse diet within the first 4 months. In contrast, sensitization was significantly more common with late food introduction: adjusted odds ratios for no solid food introductions until 4–6 months or >6 months of age were ~3. Similarly, a Finnish cohort of almost 1,000 infants examined the prevalence of sensitization to both inhalant and food allergens, and found increased rates in children with delayed food introduction [22]. Curiously, given some paradigms of oral tolerance, this did not appear to be an antigen-specific, but rather a generalized effect. Finally, the Australian Childhood Asthma Prevention Study, including ~500 healthy infants, also failed to demonstrate a protective effect of late complementary feeding on allergic sensitization, though no benefit was seen either [23].

In contrast, though not directly bearing on the question of infant solid food introduction, a very recent paper on the role of peanut consumption during pregnancy and breastfeeding deserves mention. As part of the Consortium for Food Allergy Research, a cohort of individuals (3–15 months) at high risk for peanut allergy by virtue of established milk or egg allergy was collected by Sicherer et al. [24]. More than 25% of these young children had peanut-specific IgE levels of 5 kU/l or higher – a level that the authors considered as
‘likely indicative of peanut allergy’. Furthermore, they found by multivariate analyses that maternal ingestion of peanut during pregnancy was associated with this level of sensitization (OR, 4.99; 95% CI 1.69–14.74; p < 0.004). It must be emphasized, however, that clinical allergy was not assessed. It may well be, in fact, that among high-risk populations, sensitization is very common and widely discrepant from clinical allergy as discussed above. As an additional illustration of this likely pitfall, approximately 40% of high-risk infants at 4 months of age enrolled in a randomized controlled trial of peanut flour introduction [25] (discussed further below) are sensitized, yet the large majority are tolerating regular ingestion [Lack, pers. commun.].

**Modifying the Risk of Atopic Eczema**

A New Zealand cohort study evaluated the relationship between eczema and the diversity of solid foods introduced in the first 4 months of life. The rate of recurrent or chronic eczema was high (7.5%). No information was given on allergic sensitization to foods or on other allergic disease including food allergy. They reported a positive dose relationship between the diversity of foods introduced before 4 months and the risk of eczema at 2 and 10 years [26]. They were unable to link a significant risk to a specific food (milk, egg, cereals, vegetables, fruits).

In contrast, when examining the effects of delayed introduction of complementary foods on risk of eczema, most studies report no benefit or increased risk. The Cochrane review on the optimal duration of breastfeeding identifies two qualified studies that addressed atopic eczema in the first 12 months (n = 3,618) and one at 5 years of age (n = 113) [8]. The combined analysis failed to find evidence of protection at either time point. Along with the absence of effect of delayed feeding on allergic sensitization mentioned above, the Australian Childhood Asthma Prevention Study also failed to reveal a benefit for eczema [23].

As with the risk of allergic sensitization, some studies have reported lower rather than higher risks of eczema associated with earlier food introduction. For example, in a Swedish birth cohort, regular fish ingestion before 12 months was associated with lower rates of atopic disease, including eczema, at 4 years [11]. And an increased risk of eczema was also associated with delayed solid food introduction in the German cohort discussed above [27].

**Modifying the Risk of Clinical Allergy**

Most cohort studies evaluating the role of environmental factors in the development of food allergy, including feeding practices, have relied on reported history without confirmatory food challenges or markers of strong
sensitization with generally accepted predictive value, and so are likely to overestimate the prevalence of disease. Furthermore, many studies do not distinguish between IgE- and non-IgE-mediated disease.

In their first report of high-risk infants participating in an interventional study including both maternal avoidance (third trimester and during lactation) and delayed introduction of common allergens, Zeiger et al. [20] reported a 3-fold higher combined rate of ‘food-associated atopic dermatitis, urticaria and/or gastrointestinal disease’ at 12 months in children following a standard schedule of solid food introduction. However, at 7 years of age, there were no differences in reported food allergy between these groups [3]. Another early study of a small Finnish cohort (n = 135) also found a potentially transient benefit of delayed solid foods: self-reported food allergy at 1 year was significantly lower. However, the benefit was not significant when food allergy was defined by challenge, and was not found at the 5-year follow-up [2, 8].

Several influential thought leaders raised persistent and early objections against the trend toward more conservative feeding practice recommendations [28–30], but particularly influential data have come from the comparisons of Israeli and UK Jewish populations with widely discrepant practices of peanut introduction and prevalence of peanut allergy, despite very similar rates of atopy. du Toit et al. [10] reported on approximately 10,000 children divided between the two countries and found that while the prevalence of peanut allergy in the UK group was 1.85%, the prevalence in Israel was 0.17%. The adjusted risk ratio accounting for atopy was 9.8. There was a striking inverse correlation with the early ingestion of peanut protein between the two populations, which was a median 7.1 g/ month (frequency 8×/month) in Israeli infants between 8 and 14 months and 0 g/month in the UK. Largely on the strength of this observation, a large randomized interventional study introducing peanut flour in high-risk infants is underway [25].

Further supporting the potential benefit of early allergen exposure, two very recent prospective observational studies have reported that earlier introduction of cow’s milk protein (CMP) [13] and egg [14] is protective against IgE-mediated allergy. In their prospective observational study of 13,000 infants, Katz et al. [13], found that the mean age of CMP introduction was significantly different (p < 0.001) between the healthy infants (61.6 ± 92.5 days) and those with IgE-mediated cow’s milk allergy (116.1 ± 64.9 days). Only 0.05% of the infants who were started on regular CMP formula within the first 14 days versus 1.75% who were started on formula between the ages of 105 and 194 days had IgE-mediated allergy (p < 0.001). The odds ratio was 19.3 (95% CI 6.0–62.1) for development of IgE-mediated milk allergy among infants with exposure to CMP at the age of 15 days or more (p < 0.001). Similarly, Koplin et al. [14] found in their study of 2,589 infants, that introduction of egg at 10–12 or >12 months was associated with increased risk (OR 1.6 and 3.4, respectively) compared with introduction between 4 and 6 months. This risk was found in both high- and low-risk infants and persisted after correction for multiple potential confounders.
Based on these accumulating data, several official recommendations and position statements have changed to reflect the shifting consensus. For example, the American Academy of Pediatrics, which in 2000 endorsed delayed introduction of egg, peanut, tree nuts and fish, now concludes, ‘there is no current convincing evidence that delaying solid food introduction beyond this period has a significant protective effect on the development of atopic disease... This includes... foods that are considered to be highly allergic, such as fish, eggs and foods containing peanut protein’ [31]. The ESPGHAN goes somewhat further recommending against both early (<4 months) and late (>7 months) introduction of complementary foods without respect to potential allergenicity [32].

Modifying the Course of Established Allergic Disease

A related but distinct question is what role dietary allergen exposure may have in modifying established clinical disease. This has been addressed largely outside the time of complementary feeding, in older children with persistent egg or milk allergy who have already transitioned to the family diet. For example, Allen et al. [33] surveyed approximately 200 families of older children (mean age 6.6 years) with egg allergy and concluded that strict avoidance of egg and accidental ingestion of egg did not appear to influence the acquisition of tolerance. Studies have shown that a substantial proportion (~2/3) of children with milk or egg allergy tolerate immunologically significant amounts of allergen in other foods – particularly when they have been extensively heated [34, 35]. Intentional exposure of these children to allergen in this form has been associated with immune responses that correlate with tolerance [34–36]; however, a randomized study to address this has not been reported. The immunological effects of oral exposure in those with established disease receiving oral immunotherapy may substantially overlap with those that occur as a result of more casual exposure. However, given the capacity of IgE to facilitate antigen presentation and influence adaptive immune responses, the exposure of allergen in an individual with high-affinity IgE may have significantly different effects on specific immunity [37]. In addition, because infancy is likely to be a critical period for establishing oral tolerance, earlier interventions in allergic individuals may be warranted regardless of findings in older children.

Conclusions

Food allergy is thought to be a manifestation of failed oral tolerance induction that is the result of complex interactions between gut permeability/maturity, bacterial colonization, and the timing of antigen exposure.
Complementary feeding recommendations must be informed by multiple health considerations of the infant/toddler transitioning from breast milk (or infant formula) to family food. Though randomized clinical trials are needed, the current data generally point to an increased risk of food allergy or related conditions associated with delayed introduction of solid foods, including those regarded as more allergenic such as peanut, egg and fish and regardless of infant risk. This tentative conclusion is also more consistent with current paradigms of oral immune tolerance.

References

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**Discussion**

*Dr. Fasano:* I think that you did a great job to give us a ‘twenty thousand feet up in the air’ overview, and I want to make sure that you expand some very important messages that you just convened for us. I think that there is no debate anymore that immune progression from tolerance to immune response is a generalized machinery that applies to allergy, autoimmune diseases, inflammation in general and also the concept that the final destination does not always match with clinical outcome. I think the most intriguing message that you just gave us is that in a situation of food allergy like cow’s milk protein intolerance, which we know that the vast majority of kids grow out of within a certain period of time, there are two events that seem to be really decisive in switching from a new response to tolerance. If I got the story right, basophils would go down and the T reg would go up, and these are your biomarkers. It would be tremendously helpful to understand what kind of tricks they used to outgrow this, because the same tricks can then be applied to kids that do not outgrow for example peanuts or shellfish allergies. And to my second question: cow’s milk protein intolerance, it’s something that really is not tissue specific; you start the game at the level of the intestine, but the skin can be involved as a clinical outcome, the airways can be involved, within the GI tract you can have the colon involved, but not the small intestine and vice versa. What is the tropism in terms of tissue targeting that dictates the clinical outcome? Do we know anything about that?

*Dr. Shreffler:* Regarding the first question, the basophil sensitivity to milk among those children who are more tolerant -- prior to a kind of natural high dose exposure -- is lower, probably purely reflecting differences in their IgE repertoire. It’s then further suppressed with active allergen exposure – this is what we’ve published in the context of the milk allergic children who outgrow their allergy [1]. At the same time, yes, these patients also have higher frequencies of specific Tregs, and one of the mysteries in this is how is that regulatory T cell population expanding in the absence of intentional exposure, because that study is not OIT, that’s just natural progression [2].

The antigen exposure necessary to expand regulatory T cells or -- when things go wrong -- expand the effector T cells, is probably explained by low antigen exposure to these ubiquitous antigens occurring from various routes, including skin, respiratory and occasional ingestions, etc. Sampling of dust from households and public environments reveals the presence of low levels of allergen in the environment, and I think this is likely even in the families that are doing their very best to avoid the allergen.

Why this doesn’t happen as readily for that individual sensitized to peanut or shellfish or something that’s associated with more persistent disease, or indeed why it doesn’t happen in the subset of milk-allergic children who have persistent disease, I suspect may be due to differences in that initial sensitization period -- that the IgE repertoire from the beginning is of higher affinity, is more T cell dependent, is more polyclonal, and that when that occurs it sets up a milieu that is more difficult for tolerance to then reassert itself. That would at least be consistent with the observation that allergy to nut and shellfish does tend to be more severe, and in those children with milk allergy who don’t outgrow persistence and clinical sensitivity at least weakly associate. While any child with milk allergy, even a child who outgrows by 3 or 4 years of age, may certainly have a severe reaction, on the whole these phenotypes track together, and those kids that don’t outgrow their milk allergy well into adulthood are the ones that scare us because they have very high specific to total milk specific IgEs, they have very high-affinity IgE, they have severe reactions. I think that with that kind of early insult, whatever it was, and the establishment of a robust IgE response probably pretty early on, the odds are against them from that point forward for tolerance to reassert itself. And I think in our efforts to intentionally induce tolerance, this may
Dr. Fasano: What about the tissue trophism?

Dr. Shreffler: I don’t think all that much is known. There is evidence of some shared T cell homing markers between gut and skin, and that T cells primed in one location are able to home to either site and that that might be physiologically very important. I am particularly interested in the skin route of sensitization vis à vis this retinoic acid story which I didn’t go into at all, but we have evidence that a protein in peanut can directly induce RA production. Perhaps outside of the gut -- which is generally already RA rich -- maybe that’s particularly sensitizing rather than tolerogenic. Whether or not it’s allergic, however, it should at least be inducing gut trophism. I guess one other point is that I showed you that while the basophil suppression is enhanced by antigen exposure, the T regulatory cells actually disappear from the peripheral blood once these kids start eating antigen, and so our hypothesis about that is that they probably go into the gut, but of course maybe they are apotosing or something else.

Dr. Lake: Would you want to comment on intrauterine sensitization?

Dr. Shreffler: One can measure allergen-specific IgE in cord blood, and certainly we can measure IgE very early in life. I showed that paradigm of TH2 and IgE, and I presented IgE induction as a T-dependent process. It’s very clear, however, and a good example of this is in some immunodeficiencies, that there are non-T-dependent pathways of IgE induction, and these are probably relevant outside of the immune deficiency as well. For example, the skin of kids with atopic dermatitis pumps out lots of BAFF, a factor that’s known to be sufficient to induce IgE class switching in B cells in a T-independent fashion. This suggests the hypothesis that some of the IgE that we measure early in life are not secondary to antigen exposure via the maternal bloodstream followed by an adaptive immune response in the baby. Certainly one of the hallmarks of this sort of non-T-dependent IgE repertoire would be that it would tend to have low affinity and be expressed from germline sequence without somatic mutation akin to ‘natural’ IgM antibody. Allergens are often decorated with the sort of non-mammalian glycans that natural antibody may recognize with low affinity. So, to what extent the IgE that we measure very early in life or from cord blood is truly reflective of a T-dependent, antigen-dependent process, I am not sure.

Dr. Saavedra: When you presented the data on IgE repertoire, there were various proteins that you showed in terms of potential for outgrowing. I know there is a large number of casein proteins and a relatively small number of whey proteins. Would you care to comment on the difference between casein sensitization and tolerance versus whey?

Dr. Shreffler: I think there are pretty convincing data that whey and casein fraction proteins are handled differently by the immune system. Casein is handled like particulate allergen via Peyer’s patch; casein allergens are very important sensitizers. Whey proteins, in contrast, are much more readily absorbed through the epithelium. My colleague Cecilia Berin at Mount Sinai had some very nice work together with Lloyd Mayer showing in part that the sensitization to whey proteins in an animal model might play a larger role in anaphylaxis because they are rapidly absorbed into the bloodstream [3].

There is a body of literature comparing casein and whey sensitization with respect to clinical outcomes in humans.

Dr. Mohanty: Clinically, what we see is once children developed allergy (for example cow’s milk allergy), they grow out of this allergy as the age advances. So first there is tolerance, then there is allergic manifestation, i.e. the disease, and then they grow out of it, meaning they probably developed tolerance again. In your model, is there something which can explain this?
Dr. Shreffler: I don't know about the early tolerance and then disease and then tolerance again. I think what's truer to my experience is that they may well have been getting milk in their diet but probably had some at least suspected pathology that in retrospect was probably real, such as bad eczema and you took the milk out of the diet and the eczema resolved, or much less frequently, in my experience, perhaps some chronic respiratory disease. You are saying that you take the milk out of their diet and they get better, and then they ultimately outgrow the allergy altogether. I think that is similar to the patients I am describing who pass a challenge to heated milk and once that is added to the diet and they actually get regular exposure to milk it seems to be beneficial.

Dr. Mohanty: If there is a child with a family history of allergic diathesis, instead of introducing cow's milk as a complementary food during the weaning time, can we test his/her IgE level, then give cow's milk for some time and then repeat the IgE test? If the IgE level is very high, we could then stop giving cow's milk even though the child has not developed symptoms of allergy.

Dr. Shreffler: I think that if they are tolerating cow's milk in the absence of symptoms regardless of the IgE, I would be loath to take it out of the diet at all. But if they had disease and they have IgE -- a disease that you were convinced was provoked by milk -- and now they are able to tolerate some milk protein, then I think following IgE over time and using that as a guide to expand the milk in the diet is a reasonable approach.

Dr. Jones: We have a long-term cohort, a 16-year birth cohort, where we have looked at sensitization in utero. We don't find anything predicts cow's milk or egg allergy, but peanut allergy is in fact predicted by peanut intake in the mother independent of the child intake during childhood and it's actually modified by the family history of atopy, so the question over there is relevant. If there is a family history of atopy, the peanut intake during pregnancy is a strong positive predictor of peanut allergy at 16, but if there is no family history of atopy, avoiding peanuts during pregnancy actually increases your risk 5-fold. For ryegrass, we actually don't find in utero exposures have any role, but season of birth does. So if you are born during the high ryegrass period in Tasmania and get a viral infection at that time, you have a very high risk of having RAST-positive ryegrass testing.

Dr. Shreffler: Yes, it's interesting. Scott Sicherer has a high-risk cohort of much younger patients, obviously not 16 years of follow-up, but also found evidence of more IgE sensitization with maternal exposure. The problem with that is that maternal exposure doesn't necessarily mean that the relevant route was the mother's ingestion as there might be more peanut in the home, etc.

References