

Prevention of Food Allergy

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KEY CONCEPTS

- Despite a trend toward delayed weaning, food allergies have increased in the past decades.
- Exclusive breast-feeding for the first 3 months of life may have a protective effect on allergy outcomes, but not specifically food allergies.
- There is no consistent evidence to support exclusive breast-feeding beyond 3 months of age as means to prevent food allergy or atopic disease.
- Hydrolyzed formulas in high-risk infants reduce symptoms of eczema.
- There is a need for randomized-controlled studies to test novel prevention strategies such as oral tolerance induction.

Introduction

The prevalence of IgE-mediated food allergy appears to have increased over the last few decades with approximately 3–6% of children in the developed world affected [1]. The increase in food allergy is best described for peanut allergy [2–4]. For example, in the United Kingdom three sequential studies (cohorts born 1989–2000) demonstrate an increase in the prevalence of peanut allergy from 0.6% to 1.8% over the last 10 years [3]. Food allergy is now considered a public health concern as the condition is associated with significant morbidity and occasional mortality. Although genetic factors are clearly important in the development of food allergy, the increase in food allergy has occurred over a short period of time and is therefore unlikely to be due to germ-line genetic changes alone. It seems plausible therefore that one or more environmental exposures may, through epigenetic changes, result in the interruption of the “default immunological state” of tolerance to foods. Strategies are therefore required for the prevention of food allergy: primary prevention strategies seek to prevent the onset of IgE sensitization, secondary prevention seeks to interrupt the development of food allergy in IgE-sensitized children, and tertiary prevention seeks to reduce the expression of “end-organ” allergic disease in children with established food allergy.

This chapter does not seek to replicate the many reviews in this field. Rather it aims to highlight the important

conclusions derived from these reviews and focuses on novel strategies that help advance contemporaneous thinking in this field.

Methodological challenges

In this section we examine the methodological aspects which complicate the interpretation of the many studies performed in the field of allergy prevention (summarized in Table 38.1).

Numerous studies have assessed different strategies for the prevention of food allergy. Despite this extensive body of work, findings have generally proved ineffective. The fact that no single intervention, or combination of interventions is able to repeatedly demonstrate a strong protective effect against food allergy, reflects either on the interventions themselves or alternatively, the study methods used to measure them.

A major limitation of many food allergy prevention studies lies in the study design, with few nutritional studies being randomized due to the necessary ethical restrictions which surround randomization of infants to anything but breast milk.

A second major limitation of studies in this field is the phenotypic description of food allergy, particularly for young children. Few studies make use of food challenge procedures. Whilst the determination of tolerance is adequately determined by an open food challenge, the gold standard for the determination of food allergy is the double-blind, placebo-controlled food challenge (DBPCFC). Such challenges are laborious and may be difficult to perform, particularly in young children who may be unwilling to eat unfamiliar

Table 38.1 Methodological issues known to complicate the interpretation of studies aimed at the prevention of food allergy

Issue	Problem	Recommended approach
Study design	The majority of studies in this field are observational studies.	RDBPC trials reduce unmeasured and unknown sources of bias.
Reverse causality	Early signs of suspected allergic disease (such as eczema) will result in altered feeding patterns.	If possible, trials should adopt RDBPC methodologies for food challenging.
Randomization	There are necessary ethical restraints which limit randomization to dietary interventions. This is especially so for studies involving infant milks.	Breast-feeding should always be encouraged. Studies which wish to assess the effect of complementary feeds should randomize within the breast-fed group.
Blinding of dietary interventions	Blinding of specific dietary interventions may not be possible due to safety concerns or practical limitations.	It may not always be possible to have a placebo arm to infant nutritional studies.
Determination of food allergy	Few studies make use of the oral food challenges (OFC) for the diagnosis of food allergy. The diagnosis of food allergy is therefore often inadequate both at study entry and exit. Too many studies rely exclusively on the presence of specific IgE (as determined by skin prick testing and/or specific IgE).	Aim to perform oral challenges in all participants. For children who do not undergo OFCs, <i>a priori</i> diagnostic algorithms are required which will then reach a diagnosis through the combination of history, examination, skin prick testing, and specific IgE determination.
Surrogate markers	Eczema, rhinitis, and asthma are often used as surrogate markers of food allergy.	As above
Natural history of food allergy	Tolerance is anticipated for many, but not all, childhood food allergies.	Account for natural remission rate of a disease before assessing for a study effect.
Nomenclature	There is insufficient consensus within the allergy community with respect to the terminology of common allergic conditions.	Consensus with respect to the allergy nomenclature, of common allergic disorders will greatly facilitate research in this field.
Allergy diagnosis	There is little consensus within the allergy community with respect to the ideal diagnostic criteria to be used for common allergic conditions, particularly in early childhood. For example, many studies refer to generic terms such as “allergy” or “atopy.” Definitions for each of these conditions are open to great variability.	Consensus with respect to the diagnosis of common allergic disorders is desperately required between specialist allergy organizations.
Determination of diet	The determination of food consumption is usually by retrospective Food Frequency Questionnaire (FFQ). FFQs are prone to many forms of bias.	Use should be made of prospective food diaries which have been validated for context, language, and consistency.
Dietary variables and measurement thereof	Few dietary analyses consider all variables; these include age of introduction, quantity ingested (individual and cumulative), frequency of exposure, variability of allergens, allergen processing, and concomitant breast-feeding at time of commencing complementary feeds.	Well-designed validated tools are required in order to accurately record all dietary variables.
Definitions: weaning	Use of the term “weaning” is not consistent and is usually limited to the introduction of solid foods only.	Adopt the term “complementary feeding” which incorporates any nutrient-containing food or liquid other than breast milk given to young children during the period of complementary feeding.
High-risk markers	Many studies are aimed at high-risk atopic populations. However, such populations are difficult to define.	Studies should include entire study populations (i.e. both low and high risk). At-risk populations should be defined <i>a priori</i> . Better high-risk markers are required.
Separation of specific effects when interventions are combined	Multiple interventions are often studied at different time points. For example, probiotic administration may be to mother (during pregnancy and/or breast-feeding) and/or newborn infant. This makes it difficult to determine the specific effect of each intervention at each time point.	Preliminary proof-of-concept studies need to separate the effects of each intervention.
Introduction of complementary feeds is associated with multiple variables	The early cessation of breast-feeding and introduction of complementary feeds have been associated with cultural, socio-economic factors as well as specific factors such as maternal age, formula feeding, and maternal smoking.	Regression analysis should control for as many relevant confounders as possible, especially in observational studies. This highlights the need for randomized-controlled trials.
Monitoring adherence	Monitoring of adherence to interventions, particularly dietary interventions is difficult.	Better tools for monitoring dietary adherence are required.

food/s. In addition, entry-level oral challenges cannot be performed in those children assigned to the avoidance arm of intervention studies. The true phenotype of infants at time of enrollment or exit from studies is therefore seldom certain. This limitation is particularly problematic for the diagnosis of cow's milk allergy (CMA) which is a common and frequently studied childhood allergy associated with both immediate onset IgE-mediated and delayed onset non-IgE-mediated reactions.

The most frequently used surrogate marker for the determination of food allergy is the outcome of IgE sensitization (determined by skin prick test results and/or specific IgE determination). Although IgE-mediated food allergy requires the state of "sensitization," the majority of children who are sensitized to foods are not food allergic.

Eczema is also a commonly used surrogate for food allergy. Whereas eczema has been shown to be a risk factor for the development of food allergy, not all food allergic children have eczema [5,6]. Hence, although eczema is strongly associated with food allergy, the two are not synonymous, as evidenced by studies which demonstrate an improvement in eczema but not food allergy. In addition, most studies which report an effect on eczema do not assess the severity of the eczema. Mild eczema has been shown to run a transient course when compared with moderate-severe eczema [7]. It may therefore be that studies which claim to prevent eczema are actually treating eczema (i.e. tertiary prevention) in children who entered the study with food allergy. Alternatively, study effects may be limited to the transient disease of mild eczema. Similar limitations apply to the diagnosis of asthma and rhino-conjunctivitis.

Additional limitations of the surrogate markers used for the diagnosis of food allergy include inconsistencies in nomenclature and difficulties in accurately diagnosing these conditions in infants and young children. For example, different terms are used to describe the "eczematous" condition. This results not only in disease misclassification, but may describe different immunological conditions. Indeed, the role of atopic sensitization in childhood eczema remains obscure as it is neither a prerequisite nor a uniform cause of the disease.

Nutritional studies are prone to selection bias and reverse causality. Such bias may arise when atopic families – if aware of public health recommendations – are increasingly motivated to alter dietary practices, either in their own diet or in the diet of their infants. The effects of reverse causality are highlighted in various studies and for different allergic outcomes. For example, in the Avon Longitudinal Study of Parents and Children (ALSPAC), a history of an allergic reaction to peanut was associated with prolonged breast-feeding [5]. However, when adjusted for infantile eczema by regression analysis, there was no effect of breast-feeding on the development of peanut allergy.

Childhood food allergies are dynamic with the general trend being for resolution of many but not all during the first

decade of life. This is also true for mild eczema and select asthma phenotypes. Study planning needs to take these natural histories into account prior to assessing for long-term study outcomes.

Observational studies (as most studies in this field are) are vulnerable to bias from both unmeasured, and unknown, sources. In an ideal world, study hypothesis would therefore only be assessed by randomized double-blind, placebo-controlled (RDBPC) studies. The inclusion of a placebo in nutritional studies is not always practical, or safe. Randomized-controlled studies in infants testing the early or delayed introduction of a food or foods cannot practically incorporate a placebo in the control group.

Above all, study interventions should be safe for both mother and child. Safety concerns have nonetheless arisen in select studies. For example, dietary interventions have been noted to compromise fetal and maternal well-being [8] and studies using probiotics have shown increased rates of sensitization and allergic outcomes in separate studies [9,10].

Prevention studies are often aimed at high-risk families. The high-risk population is however difficult to define. For example, approximately 10% of children without an allergic first degree relative develop allergic disease, compared to 20–30% with single allergic heredity (parent or sibling) and 40–50% with double-allergic heredity [11]. In addition, the definition of the term "atopy" is inconsistent.

Many interventions are introduced to both mother and child. This complicates the understanding of specific study effects as it is unclear whether the immunological effects were achieved pre- or postnatally or whether effects should be attributed to a single or multiple factors.

The determination of dietary intake is usually performed by Food Frequency Questionnaires (FFQs). FFQs are known to be subject to substantial forms of bias. FFQs do not always assess all relevant dietary variables such as age of introduction, recurrence of exposure, quantity (single and cumulative) of exposure, variability of allergens consumed, and allergen processing. In addition, it is often difficult to disguise those questions which relate to the specific food/s of interest. Prospective food diaries are cumbersome as they demand detailed information and effort by parents.

It is difficult to measure food allergen exposures which occur via routes other than the oral route (e.g. through an abraded skin barrier). For example, the nursing mother who ingests peanut butter is also likely to transfer this allergen to the infant through kiss and touch-contact [12,13]. In addition, it is often the nursing mother who determines consumption patterns within the household, which further increases (or decreases) the opportunity for environmental food allergen exposure to foods which the mother likes (or dislikes). A different problem arises if the intervention is one of avoidance as the elimination of one or more foods from the diet is likely to impact the diet. Such changes may be anticipated and therefore measured, or unknown and missed.

Onset of sensitization and food allergy

It remains unclear as to when prevention strategies should be implemented. It is therefore important to determine whether sensitization occurs *in utero*. Prerequisites for the development of food allergy (particularly in genetically susceptible individuals) are thought to include allergen exposure, uptake, recognition, and processing. The fact that *in utero* sensitization to foods is possible is suggested by the early clinical presentation of IgE-mediated food allergies. This is usually apparent within the first year of life. Non-IgE-mediated food-induced immunological reactions such as cow's milk-protein (CMP)-induced colitis usually present in the first year of life.

There is some data that food and aero-allergens can be transmitted via the placenta [14]. However, the analysis of specific IgE to foods in cord blood in two large birth cohort studies was unable to demonstrate measurable food specific IgE in cord blood, even in those children who subsequently developed clinical or immunological food sensitization [5,15].

Summary

Although possible on theoretical grounds, there is no firm evidence to support the hypothesis that sensitization and allergy to foods commences *in utero*.

Maternal diet (during pregnancy and/or breast-feeding) and the prevention of food allergy

In this section we examine the effect of maternal diet during pregnancy and/or lactation on the development of food allergy.

There are three studies which assess the effects (with respect to allergy prevention) of maternal dietary avoidance of one or more common food allergens during pregnancy [16–18]. In a Cochrane review, Kramer *et al.* [19] assessed the evidence for allergy prevention through prescribing an antigen avoidance diet during lactation. They include four trials involving 334 women. Their findings suggested a protective effect of maternal antigen avoidance on the incidence of atopic eczema during the child's first 12–18 months of life. There was no effect on asthma or rhinitis. They however also noted the methodological shortcomings in all three trials and argued for caution in applying these results. Most importantly, one trial reported that a restricted diet (egg and CMP) during pregnancy was associated with both maternal and fetal nutritional compromise.

Given the uncertainty of these findings, and potential safety concerns, specialist allergy organizations do not recommend the avoidance of either egg or milk during pregnancy [20–25]. However, there are recommendations for the avoidance of peanut in high-risk scenarios by both the American Association of Pediatrics (AAP) [26] and the UK Government

Department of Health (DoH) [27]. This recommendation was not evidence based and came about as a response to the public health concern of peanut allergy. There are no studies which assess effects of modifying maternal diet during lactation only. There are however studies which modify the maternal diet during pregnancy or both pregnancy and lactation; these have not shown a protective role against infant food allergy through maternal dietary avoidance of cow's milk, egg, and fish during either pregnancy and/or breast-feeding. In addition, the ALSPAC study showed no effect of maternal peanut consumption in pregnancy or lactation on the development of immunological or clinical reaction to peanuts on follow-up at 4–6 years of age [5].

Breast milk contains low concentrations of dietary proteins which are present in maternal serum. Indeed, β -lactoglobulin is found in the breast milk of 95% of mothers consuming cow's milk during lactation. Whether at-risk infants are protected by the many beneficial immunological properties of breast milk or put at risk by this low-dose allergen exposure is an ongoing debate. There are studies which modify the maternal diet during both pregnancy and lactation. Neither the study by Hattevig *et al.* [7] nor the study by Herman *et al.* [28] demonstrate a protective role against infant food allergy through maternal dietary avoidance of cow's milk, egg, and fish during either pregnancy or both pregnancy and lactation. The study by Herman *et al.* did however note effects for eczema.

Summary

Manipulation of the maternal diet during pregnancy and/or breast-feeding has not consistently been shown to exert protective effects on the development of allergy; however preventative effects are noted for eczema. Such strategies carry the risk of nutritional compromise for both mother and child.

Complementary infant feeding and the prevention of food allergy

In this section we examine the effect of complementary feeding on the development of food allergy.

The World Health Organization (WHO) now recommend that the term "weaning" be replaced by the term "complementary feeding" which incorporates any nutrient-containing food or liquid other than breast milk. Most studies in this field consider weaning to be the introduction of solid foods only. However, the biophysical properties of allergens are complex and there is no reason to believe that the allergenic potential of liquid feeds is different from that of solid or semi-solid feeds. For example, both cow's milk and hen's egg allergy are common childhood allergies despite being ingested as liquid and solid, respectively. An infant who is breast-fed whilst receiving cow's milk formula (CMF) supplementation is no more or less weaned than a breast-fed

infant who is fed rice cereal mixed with expressed breast milk. It is therefore arbitrary to restrict the usage of the term “weaning” to solids.

Breast milk provides a rich and favorable source of immune-regulating substances and possesses numerous other qualities which have the capability of directly influencing allergic disease expression. For example, breast milk regulates food antigen absorption and processing which may delay or prevent the development of food allergy. Breast milk has also been shown to decrease lower respiratory tract infections (LRTIs) in the first year of life and LRTIs are known risk factors for the development of asthma. That worldwide breast-feeding is initiated in only 60–80% of newborns and exclusive breast-feeding rates remain below WHO targets.

There are numerous health care specialist allergy organizations which offer advice with respect to infant feeding in at-risk infants [20–24]. Whilst there is consensus that breast milk remains unchallenged as the milk of choice for all infants, advice with respect to the duration of exclusive breast-feeding and the avoidance of common food allergens differ between organizations.

Studies which support a protective effect of breast-feeding over CMFs date back to the 1930s when Grulee and Sanford demonstrated a protective effect of breast-feeding on the development of eczema in the first 12–48 months of life in a large ($n \approx 20,000$) observational study [29]. Not all of the observational studies which followed supported these early findings. In a 2007 review by the Paediatric Section of EAACI, Muraro *et al.* [30] suggested an overall protective effect (for at-risk children) of exclusive breast-feeding during the first 3 months of life on atopic eczema and asthma, but not childhood allergic rhinitis.

While exclusive breast-feeding for 3 months may protect against the development of allergy taken in the context of the numerous studies done in this field, the consensus however is that prolonged exclusive breast-feeding beyond 3 months of age has not been shown to consistently protect against the development of food allergy, or atopy. Kramer *et al.* [31] performed a WHO commissioned systematic review of the available evidence concerning the effects of exclusive breast-feeding for 6 months versus exclusive breast-feeding for 3–4 months followed by mixed breast-feeding (complementary liquid or solid foods with continued breast-feeding) to 6 months, on eczema, asthma, and other atopic outcomes. This extensive review covers 20 independent observational studies. They were unable to establish evidence for a significant reduction in the risk of atopic eczema, asthma, or other atopic outcomes amongst those infants who were exclusively breast-fed for 6 months compared with those exclusively breast-fed for 3–4 months followed by mixed feeding.

It is therefore surprising that the WHO [32] recommendations use the justification of reduction in atopy to support exclusive breast-feeding for the first 6 months of the infant's life. While there are other beneficial health effects

of prolonged exclusive breast-feeding, prevention of allergy does not provide a justification.

Kramer *et al.* [33] in a recent large ($n = 13889$) cluster randomised trial indicate that the experimental intervention to promote breastfeeding did not reduce the risk of asthma, hay fever, or eczema at age 6.5 years despite large increases in the duration of exclusivity of breast feeding; nor did the intervention succeed in reducing the prevalence of positive skin prick tests. Indeed, there was a suggestion that atopic sensitisation by skins tests to inhalent allergens was increased in the intervention group.

There are only two randomized studies looking at the introduction of CMP formula against exclusive breast-feeding on the development of food allergy and atopy. Lucas *et al.* [34] in a large ($n = 777$) randomized interventional study of premature infants, compared the effects of human breast milk, standard preterm formula, and nutrient-enriched preterm formula. Interestingly, at 18 months after term there was no overall difference in the incidence of food-allergic reactions between dietary groups, although a subgroup effect was noted for the group of infants with a family history of atopy. Similarly, in a large ($n = 1693$) randomized intervention study of term infants, De Jong *et al.* [35] found that early (first 3 days of life) high-dose exposure to CMP (as frequently occurs in nurseries) was not associated with an increase in allergic disease or symptoms. In addition, no increase in sensitization or allergy to CMP was found between the groups up to 5 years of age.

There are indeed some observational studies which demonstrate an increased risk in the development of allergic disorders in breast-fed infants. In a large ($n = 1037$ children) observational study, Sears *et al.* [36] followed up children until 21 years of age. They found that breast-feeding (for at least 4 weeks) did not protect against childhood atopy and asthma. Indeed, significantly more breast-fed children were atopic to common aero-allergens at the age of 13 than non-breast-fed children. Breast-feeding also increased the likelihood of asthma at age 9 and 21 years. Findings were similar when breast-feeding was considered over longer periods (8–12 weeks). Exclusive breast-feeding did not offer any protection against atopy and there was even a suggestion that the risk of atopy was increased. Likewise, in the large Multicenter Allergy Study (MAS) observational birth cohort ($n = 1314$ infants born in 1990), Bergman *et al.* [37] found that each month of breast-feeding elevated the risk of developing atopic eczema in the first 7 years by approximately 3%. It was noted, however, that breast-feeding persisted for longer if at least one parent had eczema, the mother was older, did not smoke in pregnancy, or the family had a high social status. Reverse causality could not be ruled out in this study.

The WHO recommendations that exclusive breast-feeding be continued until 6 months of age is a change to their previous recommendations and different from the 1999 joint

European Allergy Statement which recommended exclusive breast-feeding for between 4 and 6 months. Interestingly, there has, since 1975, been a significant trend in developed countries toward the later introduction of solid foods. For example, in the United Kingdom, the proportion of infants given solids by 8 weeks of age has decreased, 49% in 1975, 24% in 1980 and 1985, and 19% in 1990 [38]. It is interesting that this decrease to a third of what it was has coincided with a 3-fold increase in allergy in children [39]. Reasons for differences in weaning are complex and early weaning has been associated with cultural, socio-economic, as well as specific factors such as maternal age, formula feeding, and maternal smoking. All of these factors need to be controlled for in study analyses.

A review of the evidence for the relationship between the early (defined as less than 4 months of age) introduction of solid foods to infants and the development of allergic disease was recently performed by Tarini *et al.* [40]. Thirteen studies met their criteria for review, of which only one was a controlled study. Studies were not limited to at-risk study populations. They concluded that there was insufficient evidence to suggest that, on its own, the early introduction of solids to infants was associated with an increased risk of asthma, food allergy, or allergic rhinitis. They noted the consistent association between the persistence of eczema and the introduction of solid foods before 4 months of age that is supported by long-term follow-up studies and the dose-dependent nature of the association.

Fergusson *et al.*'s [41] article is the only study to report an increased risk of persistent eczema with the early introduction of solids. They reported a 2.9 times greater risk of chronic or recurrent eczema amongst children fed four or more solids before 4 months of age compared with those not fed solids before 4 months of age. This difference was still apparent at 10 years of age. When they assessed the effect of exposure to individual foods such as cow's milk, egg, cereals, vegetables, meat products, or fruits they found no increased risk of developing atopic dermatitis (AD). Zutavern *et al.* [42] more recently conducted a large multicenter study which controlled for the effects of reverse causality whilst assessing for the effect of early life diet on allergy outcomes. They found no evidence of a protective effect of late introduction of solids on the development of pre-school wheezing, transient wheezing, atopy, or eczema. There was no evidence for a protective effect of the delayed introduction of solids beyond 4 months of age on the development of sensitization to foods. On the contrary, there was a statistically significant increased risk of eczema in relation to late introduction of egg and milk. The late introduction of egg was also associated with a non-significant increased risk of pre-school wheezing.

Although exclusive breast-feeding does not have proven effects in the prevention of allergy, there have been numerous studies examining the protective effects of different types of formulas especially CMP-hydrolysates as a substitute

for breast milk where the mother is unable to or chooses not to breast-feed. There are several studies and a meta-analysis of the evidence for the role of infant formula in the prevention of allergic disease in high-risk infants who are unable to breast-feed. Cochrane review by Osborn *et al.* [43] found no evidence to support feeding with a hydrolyzed formula for the prevention of allergy compared to exclusive breast-feeding. For high-risk infants who are unable to be completely breast-fed, they found limited evidence that prolonged feeding with a hydrolyzed formula compared to a CMF-reduced infant and childhood allergy and infant CMA. The general consensus among the reviews is that the use of hydrolyzed milk formula in at-risk infants offers at least some protection against allergic disease, and in particular eczema. These findings are reflected in the recommendations of specialist allergy organizations [20–24].

One recent study in this field is the German Infant Nutritional Interventional (GINI) study [42,43]. This is a large ($n = 2252$) randomized multicenter study in which von Berg *et al.* allocate high-risk infants to one of four milks; CMF, partially hydrolyzed whey formula (pHW-F), extensively hydrolyzed whey formula (eHW-F), or extensively hydrolyzed casein formula (eHC-F). A significant reduction in the incidence of AD was achieved at 1 and 3 years of age with the eHC-F and the pHW-F. The greater reduction in eczema at 1 year of age in high-risk children with a pHW-F and eHC-F rather than with an eHW-F is difficult to explain. In this study, hydrolyzed formula did not protect against wheezing. The clinical benefits demonstrated by the GINI study are convincing. However it remains unclear whether dietary modification has truly prevented allergic disease. The GINI study [44,45] was not able to clearly define the endpoint of food allergy by DBPCFC as many parents declined. The reduction in eczema could therefore either be due to the primary prevention of eczema through dietary modification or alternatively reflect the beneficial effect of removing CMP from the diet of infants with concomitant eczema and milk allergy.

Soy formulas have long been used as CMF alternatives. In a recent Cochrane review, Osborn *et al.* [46] found three studies which met their inclusion criteria. They concluded that, on current evidence, the use of soy formulas could not be recommended for the prevention of allergy or food intolerance in at-risk infants. No study demonstrated an increase in soy allergy. There is also no evidence to support the use of "other" mammalian milks for the prevention of food allergy.

Summary

There is some evidence of a protective effect against the development of allergy in high-risk infants when exclusively breast-feeding for the first 3 months of life. There is no convincing effect noted beyond 3 months of life in both high-risk infants and normal infants. Some studies suggest that prolonged exclusive breast-feeding may increase the risk of

allergies, although reverse causality may be an explanation. The use of CM-hydrolysates in high-risk infants shows amelioration of eczema – but not food allergy – at 1 and 3 years of age (in the GINI study). There is no evidence that hydrolyzed formulas prevent against the development of other allergies. There is no evidence to support the use of soy formula or “other” mammalian milk formula for the prevention of allergy.

Combined maternal and infant dietary measures and the prevention of food allergy

It seems intuitive that of all dietary interventions aimed at the prevention of food allergy the combined approach should offer the greatest hope as it covers many routes of allergen exposure at immunologically vulnerable time points.

In a Cochrane review, Kramer *et al.* [19] assessed the evidence for the prevention of allergic disease through maternal dietary antigen avoidance during pregnancy or lactation, or both. Their analysis found that the prescription of an antigen avoidance diet to high-risk woman during pregnancy was unlikely to substantially reduce her child’s risk of atopic disease.

There are two randomized studies which adopted a multi-intervention approach. Zeiger *et al.* [47] in a study of 165 mother/infant pairs randomized participants to either a prophylactic group (*maternal avoidance of cow’s milk, egg, and peanut during the last trimester of pregnancy and lactation, and infants diet free of cow’s milk until age 1 year and using a hydrolysate formula as supplement, egg until age 2 years, and peanut and fish until age 3 years*) or a control group (*following standard feeding practice*). Findings demonstrate a significant reduction in cow’s milk sensitization and eczema before the age of 2 years but no significant reduction in food allergy, AD, allergic rhinitis, asthma, any atopic disease, lung function, food or aero-allergen sensitization or serum IgE level at 7 years of age. No difference in skin prick testing or specific IgE testing was shown for the other food allergens tested, including peanut, which was the most common skin test-positive food allergen at 7 years of age. This indicates that the beneficial effect of the dietary interventions was mainly in reducing CMA.

Arshad *et al.* [48] in a study of 120 infants randomized participants to either a prophylactic group (*breast-fed with mother on a low allergen diet or given an extensively hydrolyzed formula and house dust mite reduction*) or a control group (*who followed standard UK DoH advice*). Findings demonstrate a reduction in allergic disease (asthma, atopy, rhinitis, and eczema) at least for the first 8 years of life in the prophylactic group. Repeated measurement analysis, adjusted for all relevant confounding variables, confirmed a preventive effect on asthma, AD, rhinitis, and atopy. The protective effects were primarily observed in the subgroup of children with persistent disease (symptoms at all visits) and in those with evidence of allergic

sensitization. Study powering did not allow for the assessment of food allergy at 8 years of age, but earlier transient effects were noted.

Summary

There are randomized trials which adopt a multi-intervention approach (dietary modification of both maternal diet – during pregnancy and/or lactation – and infant diet) that have demonstrated a reduction in allergic disease. Whilst findings in one study were transient and no longer observed at 7 years of age, in a second study, the effects in allergy reduction were still observed at 8 years of age. The effects with respect to a reduction in food allergy appear to predominantly apply to CMA. Caution is required prior to the recommendation of such interventions due to the potential for nutritional compromise in both mother and child.

Routes of sensitization, cross-sensitization, and oral tolerance induction

Until recently, preventive strategies have focused on oral exposure to foods. However, the oral route of exposure is not the only route as exposure to food allergens may occur through aerosolized allergen exposure (e.g. fish and milk cooking vapors) or via the skin (as detailed above). The ALSPAC study [5] followed a large cohort of children ($n = 13,971$) from birth; the results of this study showed a positive association between peanut allergy and eczema, and an even greater association with an oozing or crusting skin rash. They also found an increased use of skin preparations using peanut oil in children with peanut allergy (this was limited to cutaneous rather than oral exposure). The observations support the occupational health findings in adults that sensitization may occur through contact with the skin, particularly through abraded skin.

There is a significant body of evidence in animal models that a single oral dose of antigen is sufficient to induce oral tolerance [49–51]. This phenomenon has been demonstrated for different antigens and in different experimental models. The data is consistent; uniformly showing that a single dose of oral protein administration effectively causes immunological tolerance and prevents the expression of related clinical disease.

Poole *et al.* [52] in a large prospective cohort study in Colorado ($n = 1612$) found an association between age at initial exposure to cereal grains and the development of wheat allergy. Their data suggested that delaying introduction of cereal grains until after 6 months was not protective against development of wheat allergy, but that it may in fact increase the child’s risk of wheat allergy. This study excluded children with celiac disease (positive tissue transglutaminase autoantibodies) and controlled for family history of allergy, prior food allergy, breast-feeding duration, and whether the child was breast-fed when first exposed to cereals.

There are no interventional studies that examine the potential role of oral tolerance induction to foods in childhood. There is one adult human study that showed that feeding key-hole limpet hemocyanin (KLH) resulted in immunological tolerance to KLH antigen [53]. Ecological data suggests that African, Asian, and Middle Eastern countries [54] where peanuts are consumed throughout pregnancy and early childhood have low rates of peanut allergy compared to Western industrialized societies such as the United Kingdom and United States where peanut allergy is high despite peanut avoidance during pregnancy and infancy. However, differential predisposition to atopy due to both genetic and environmental factors could however explain these differences.

The high prevalence of peanut allergy in the United Kingdom occurs despite DoH recommendations which advocate avoidance of peanut during pregnancy, breast-feeding, and the first 3 years of life in high-risk children. Recent data suggests that the average age for peanut introduction in the United Kingdom is at 33 months as opposed to 12 months in 1985. The US National Institute of Health and Immune Tolerance Network (NIH/ITN) sponsored interventional study (LEAP Study) is currently underway and seeks to randomize infants less than 11 months of age with risk factors for the development of peanut allergy (moderate-severe eczema and/or egg allergy) to either peanut consumption or avoidance. A final assessment for peanut allergy will be made by oral food challenge at 5 years of age.

There are observational studies to other foods that lend weight to the hypothesis of tolerance induction through early oral exposure. A large observational cohort of children, by Poole *et al.* [52] demonstrated that delaying the initial exposure to cereal grains until after 6 months may increase the risk of developing IgE-mediated wheat allergy. In a population-based observational study, Saarinen *et al.* [55], fish and citrus allergy was determined at 3 years of age by oral food challenge. They then found no difference in the cumulative incidence of fish and citrus allergy at 3 years of age between children with fish introduced early or late (after 1 year of age).

Summary

Recent observational and animal studies raise the question of whether sensitization to food antigens may occur via the cutaneous route. There is a body of literature in animal models which demonstrates the effect of tolerance induction following early high-dose food allergen consumption. Human trials are awaited.

Unpasteurized milk and the use of probiotics and prebiotics

It is hypothesized that the increase in allergic disease may be due to a relative lack of microbial stimulation of the infantile

gut immune system. This is in keeping with other observations which provide support for the “hygiene hypothesis” whereby dietary, or other immune-modulating factors associated with the anthroposophic lifestyle, lead to lower rates of allergic disease [56].

Observations from rural environments suggest an inverse association between consumption of farm-produced dairy products and the prevalence of allergic disease. Waser *et al.* [57] conducted a cross-sectional multicenter study, which demonstrated that the consumption of farm milk might offer protection against asthma and allergy. These associations were independent of farm-related co-exposures and other farm-produced products, but were not independently related to any allergy-related health outcome. Similarly, Perkins *et al.* [53] conducted a two-stage cross-sectional study which demonstrated that unpasteurized milk might be a modifiable influence on allergic sensitization in children. The effect was seen in all children, independent of farming status.

Other strategies have sought to alter the commensal gut flora either directly through the administration of living micro-organisms (probiotics) or indirectly through the provision of non-digestible growth-enhancing substrates (prebiotics). There are many variables between studies performed in this field; these include probiotic strain and viability, dose, and duration. In addition, not all studies treat both mother (during pregnancy and/or breast-feeding) and child. Hence, clinical trial results from one probiotic strain in one population cannot be automatically generalized to other strains or to different populations. There is also great variability with respect to patient groups recruited in trials to date. Boyle *et al.* [58] published a review in 2005 of the evidence for the use of probiotics in the management of allergic disease. They found evidence for the use of probiotics in the treatment of eczema, but the level of evidence regarding the role of probiotics for the prevention of eczema was “weak.”

More recently, Kukkonene *et al.* [59] in a large randomized trial ($n = 925$) assessed the combined role of prebiotics (*galacto-oligosaccharides*) and probiotics (four bacterial strains) in the prevention of allergic disease in a high-risk population. They randomized pregnant women to probiotic or placebo for 2–3 weeks before delivery; their infants received the same intervention or a placebo for 6 months. Results indicate that the prebiotic-probiotic combination treatment, when compared with placebo, showed no effect on the cumulative incidence of allergic disease at 2 years of age. However, the prebiotic-probiotic combination treatment did reduce eczema and atopic eczema (in both IgE- and non-IgE-sensitized children). Taylor *et al.* [10] randomized high-risk newborns ($n = 231$) to either receive *Lactobacillus acidophilus* or placebo daily for the first 6 months of life. They were unable to demonstrate a significant difference in eczema between the groups at 6 and 12 months of age, and found that the proportion of children with positive skin prick tests and eczema was significantly higher in the probiotic group.

Whether probiotic-induced microbiota changes – and associated clinical effects – persist after administration ceases remains unclear. For example, in a study by Kalliomaki *et al.* [9,60] initial findings at 4 years of age suggested a reduction in eczema, rhinitis, and asthma, however at 7 years of age, the overall risk for developing eczema remained lower in the *LGG* probiotic group whilst allergic rhinitis and asthma were more common. Interestingly, both the Kukkonene *et al.* and Kalliomaki *et al.* studies find the preventive effect on eczema not to be associated with IgE changes [9,59].

Boyle *et al.* [61] recently highlighted the known and theoretical safety concerns of probiotics; these include infection, deleterious metabolic activities, immune deviation, excessive immune stimulation, and microbial resistance.

It has been shown that infant formulas which are fortified with prebiotics can bias the microbiota to more closely resemble that of breast milk (the so-called “bifidogenic” effect). The clinical relevance of these prebiotic-induced changes remains unclear. Cochrane reviews into the use of pre- and probiotics in the prevention of allergy are currently underway.

Summary

Observational studies suggest that the consumption of unpasteurized milk may reduce the prevalence of allergic sensitization and disease. There are safety concerns regarding unpasteurized milk and this cannot therefore be recommended for the prevention of food allergy. Although some studies do show that the use of probiotics (and in one study a mixture of both pro- and prebiotics) reduces eczema, these effects are not consistent in all studies and are not associated with a reduction in atopy. Currently neither prebiotics nor probiotics can be recommended as a strategy to prevent food allergies or other allergic disease, and safety concerns need to be considered.

Nutritional supplements

There are ecological observations which note that the geographical distribution of allergy prevalence is linked with regional dietary practices [62]. In recent years, there has been a focus on the role of vitamins, antioxidants, fruits, and vegetables, as well as fatty acid intake on the prevention or treatment of allergies.

(a) Fatty acids: Dietary lipids, especially n-3 and n-6 long-chain polyunsaturated fatty acids (LCPUFAs) regulate immune function, and may modify the adherence of microbes in the mucosa thereby contributing to host–microbe interactions. There are studies in this field which demonstrate a positive effect with respect to the prevention of allergies, however outcomes are inconsistent. Peat *et al.* [63] randomized 616 high-risk pregnant mothers (at 36 weeks gestation) to either an intervention group (omega-3-fatty acid supplementation and house dust mite reduction measures) or placebo. They demonstrate a reduction in the outcomes for dust mite sensitization and cough (in atopic children only)

for infants in the intervention group. No significant differences in wheeze were found with either intervention. There was however limited perinatal intervention in this study. Kull *et al.* [64] in a large prospective birth cohort assessed for the effect of fish (a rich source of omega-3 fatty acids) consumption on allergy outcomes in a large prospective birth cohort. After controlling for confounding factors (parental allergy and early onset eczema or wheeze), regular fish consumption during the first year of life was associated with a reduced risk for allergic sensitization to foods by age 4 years. It is unclear whether such an effect could be explained by oral tolerance induction to food proteins or whether omega-3 fatty acids could have a generic anti-allergic effect. Negative study findings include those by Almqvist *et al.* [65] who conducted a large ($n = 516$) randomized, placebo-controlled trial in high-risk children and found that dietary fatty acids (in the first 5 years of life) did not reduce the risk of asthma or allergic disease at 5 years of age. Despite these conflicting findings, many infant formulas are supplemented with LCPUFAs such as *arachadonic acid* and *docosahexaenoic acid*.

(b) Vitamins: Dietary vitamins have potent immune-modulating effects. It has been possible to study the effect of vitamin supplementation in young children with respect to allergy outcomes, as many countries advocate routine vitamin supplementation during early childhood. Separate studies in Finland [66] and the United States [67] observed an increased association between vitamin D supplementation in infancy and atopic disease. However, study outcomes were restricted to rhinitis in adulthood in the first study, and select subgroups in the second study; asthma in black children and food allergies (as defined by a medical professional) in the exclusively formula-fed population.

Kull *et al.* [68] in a large ($n = 4089$) prospective birth cohort investigated the association between the supplementation of vitamins A and D (administered in either a water- or peanut-oil-based vehicle) during the first year of life and the outcome of allergic disease up to 4 years of age. Children supplemented with vitamins A and D in the water-soluble vehicle during the first year of life had an almost 2-fold increased risk of asthma, food hypersensitivity (determined by parental questionnaire), and sensitization (to common food and airborne allergens) at age 4 years, when compared with those receiving vitamins in peanut oil. There are various possible explanations for these findings. Vitamin A and/or D may protect against the risk of developing allergy; the study findings would then hinge on better absorption of vitamins A and D from the oil-based vehicle than from a water-based vehicle. Alternatively, vitamin A and/or D may actually increase the risk of the development of allergic disease; the absorption of vitamin A and/or D would then need to be superior when the vitamins were administered in the water-based vehicle. Systemic uptake was unfortunately not measured in this study. It is not known how the rates of allergy in

the two study groups compare with children who had not received vitamin supplementation at all (less than 2% of children in this cohort did not receive vitamin supplementation). It may also be that vitamin A and/or D has no effect on allergy outcomes and the effects observed are due to the use of peanut oil itself. However, the fatty acids in peanut oil are strongly biased toward the pro-inflammatory omega-6 fatty acids in a ratio of omega-6:omega-3 fatty acids of 34:1. Were this effect to be significant, a higher rate of allergy would have been expected in the group of children who received the oil-based supplement. It is therefore difficult to interpret these findings.

(c) Antioxidants and trace elements: Antioxidants are free radical scavengers shown to decrease inflammatory processes. There are no interventional studies which assess the effect of antioxidant supplementation on the prevention of food allergy; however, ecological observations suggest that the higher intake of fresh fruits and vegetables in certain European countries is associated with a decreased prevalence of food allergy [62]. In addition, preliminary findings from the ALSPAC cohort suggest that low cord blood selenium and iron may be associated with a higher subsequent risk of persistent wheeze and eczema [69].

Summary

Randomized-controlled studies provide conflicting results with respect to LCPUFA supplementation for the prevention of allergy. Studies which show a positive effect do so for different allergic disease outcomes. Observational studies which examine the effect of vitamins A and D supplementation during the first year of life suggests an increased rate of sensitization and allergy at 4 years of age, but only when administered in a water-soluble vehicle. It remains unclear as to why vitamins A and D supplementation in different vehicles should exert different clinical effects.

Ecological observations, and preliminary studies, suggest that the higher intake of foods rich in antioxidants may confer protection against allergy outcomes. Although the role of nutritional supplements for the prevention of allergy is interesting, further randomized interventional studies are required.

Conclusions

The natural history of food allergy suggests “plasticity” within the developing immune system as many common food allergies (such as egg and milk allergy) are outgrown. Indeed, the switch from a state of allergy to tolerance may even occur during the first few years of life. Turcanu *et al.* [70] demonstrated that the resolution of peanut allergy was accompanied by a reversal of the Th2- to Th1-skewed, allergen-specific, immune response. These findings are encouraging as it raises the possibility that immune responses are susceptible to prevention strategies.

The conventional wisdom is that early exposure to allergenic food proteins during pregnancy, lactation, or infancy leads to food allergies, and that prevention strategies should aim to eliminate allergenic food proteins during these periods of “immunological vulnerability,” especially in high-risk subgroups. There is some evidence to support the use of dietary interventions in high-risk pregnant and/or lactating women, especially for the outcome of atopic eczema. Such interventions may however compromise maternal and fetal nutrition. Exclusive breast-feeding for at least the first 3 months of life offers some protection against allergic disease in high-risk infants. The protective effect of exclusive breast-feeding beyond 4 months of age remains uncertain. For high-risk infants who are not exclusively breast-fed, or where supplementation of breast-feeding is required, the use of hydrolyzed formula may offer some protection against the development of eczema. The findings of dietary interventions such as LCPUFAs, antioxidants, pre- and probiotics, and vitamin supplementation are unconvincing, inconsistent, or not adequately tested. There are safety concerns surrounding some of the interventions trialed to date.

Future studies will need to overcome the methodological challenges detailed in this chapter, many of which are unique to this field of research. Better markers are required to identify high-risk populations, as not all children who develop food allergy are born to atopic families. With current advances in the field of gene–environment interactions, it may also be that future studies need to focus their interventions at specifically defined groups of children, whose genotyping identifies them as being at-risk of (or protected from) specific environmental exposures.

Finally, in order for the field of food allergy prevention to significantly advance, strategies will need to be put to the test using rigorous study design methodologies.

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