Early Introduction of Foods for Food Allergy Prevention

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Opinion statement

The identification of food allergy prevention strategies has become an important public health issue given the increase in hospital presentations for food allergic reactions in young children. In particular, there has been an increasing interest in whether the timing of introduction of solids (particularly allergenic solids such as egg and peanuts) plays a role in development of early-onset food allergy. To date, research in the area has primarily been limited to observational birth cohort studies, which have generated data to suggest that delayed introduction of allergenic solids may actually increase rather than decrease the risk of food allergy. However, findings from these studies must be viewed with caution since it is difficult to eliminate the potential for confounding factors to generate spurious associations between infant feeding choices and food allergy risk. The emergence of a number of in progress randomised trials of early introduction of allergenic foods is likely to contribute significantly to understanding of this area as results come to light. This review discusses the current evidence for a role of early introduction of foods in the prevention of food allergy, including emerging results from the first clinical trials, and discusses the implications of these findings for population guidelines and for further research.

Introduction

The underlying theory driving research and clinical practice regarding the relationship between infant feeding and food allergy has undergone a radical

change over the last 10 years. Previously, the predominant hypothesis was that food allergy might be prevented by complete avoidance of allergenic foods

during the period of immune development. More recently, the focus has shifted to a hypothesised potential for tolerance induction through allergen exposure at appropriate times and doses in early life. Throughout this period, however, there has

been a persistent belief that infant feeding patterns are likely to influence the development of food allergy, with an increasing awareness that this is likely to occur in conjunction with other underlying genetic and environmental risk factors.

Infant feeding guidelines – history and recent changes

Over the last 50 years there have been significant changes in recommendations regarding the age at which solid foods are introduced to infants, ranging from around 3 months prior to the mid-1970s to after 6 months in the early part of this century [1]. The trend to recommend delaying solid introduction predated the initial apparent rise in food allergy but accelerated in parallel with rising rates, suggesting a potential link between the two.

Initial recommendations to delay the introduction of solid foods beyond 4 months of age, introduced in the 1970s, were based on concerns about a reported rise in the incidence of coeliac disease at a time when wheat was being fed to the majority of infants by age 3 months [2]. At the time it was believed that delaying the introduction of solids after 4 months would decrease the perceived rising incidence of coeliac disease. Further modifications to feeding guidelines specifically aimed at preventing allergic disease were introduced in the 1990s and 2000s, which recommended delaying the introduction of allergenic foods such as egg, cow's milk and peanuts until after at least 1 year. In one of the more extreme examples, UK guidelines for infants with a family history of allergy recommended that peanuts should be avoided by mothers during pregnancy and lactation, and by infants until 3 years of age [3].

Recently, in response to both the emerging evidence from observational studies and the supportive evidence from rodent trials, specialty allergy bodies around the world began revising guidelines to remove previous advice to delay the introduction of allergenic foods and avoid these foods during pregnancy and while breastfeeding. These include the American Academy of Pediatrics' revised guidelines that state there is currently no evidence to recommend maternal dietary restrictions during pregnancy or breastfeeding or delaying introduction of solids including allergenic foods after 4–6 months for the prevention of allergy [4]. Current guidelines from the Department of Health in the UK recommend exclusive breastfeeding for 6 months and avoidance of potentially allergenic foods (peanuts, other nuts, seeds, milk, eggs, wheat, fish or shellfish) until after 6 months of age [5]. In Europe, the European Society of Pediatric Allergy and Clinical Immunology and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) have produced joint guidelines. These recommend exclusive breastfeeding for 4–6 months and introducing gluten between 4 and 7 months to reduce the likelihood of developing wheat allergy [6]. In Australia, the peak allergy specialty body guidelines (ASCIA; the Australasian Society of Clinical Immunology and Allergy) recommend introducing solid foods from 4 to 6 months of age and do not recommend delaying the introduction of allergenic foods [7].

The lack of strong evidence in the area is reflected in the myriad different infant feeding guidelines aimed at preventing allergy, with infant feeding guidelines from 18 countries around the world summarised in a review by Grimshaw and colleagues in 2009 [8]. These guidelines, focused specifically on allergy prevention, are sometimes in disagreement with more general infant feeding advice provided by governments and the World Health Organisation (WHO). The WHO recommends exclusive breastfeeding for the first 6 months of life, followed by breastfeeding alongside complementary foods up to 2 years of age [9], as a global public health recommendation. However, research into the role of infant feeding in allergy prevention has been largely limited to developed countries. The current evidence for a potential beneficial effect of early introduction of allergenic foods between 4 and 6 months of age for prevention of food allergy is thus derived from studies in developed countries. Food allergy appears to be more common in developed countries, and is also relatively more important as a public health issue in these countries. The issues affecting child health in developing countries and risks of early introduction of allergenic foods compared with potential benefits differ substantially. Promotion of exclusive breastfeeding for at least 6 months in developing countries remains vitally important in the context of preventing illnesses caused by contaminated food and water and malnutrition. However, the lack of consensus between various peak bodies with regards to infant feeding guidelines is likely to have a detrimental effect on effective public health policy in this area due to the potential for confusion amongst consumers and asymmetrical uptake. This possibility has recently been highlighted by Tey et al. [10] who found that during the recent time of infant feeding guideline revision in Australia, those without a family history of food allergy as well as those from a higher socioeconomic status were more likely to respond to changes.

Development of immunological tolerance to foods and implications for promoting tolerance

In a normal state of infant health, the immune system is predisposed towards development of tolerance (or non-responsiveness) to food proteins when exposure occurs through the oral route. Understanding of the mechanisms underlying the development of oral tolerance has relevance to understanding food allergy; however, to date, information on this process is largely limited to studies using animal models. Three immunological hypotheses have been identified by which tolerance is thought to develop following oral exposure to food antigens: (1) antigen feeding leads to deletion of T cells specific to food antigens; (2) anergy of these cells (whereby the population of cells are maintained but do not respond to the antigen); or (3) active suppression of immune responsiveness by T regulatory cells [11]. In fact, in humans a combination of all three mechanisms may be involved in development and maintenance of tolerance to foods.

There is some evidence that both antigen dose and route of administration affect the development of oral tolerance. In one murine model using

mice transgenic for a T cell receptor against a peptide from ovalbumin (OVA), oral tolerance could be induced by feeding either a single high dose of OVA or repeated lower doses; however, the mechanisms mediating this tolerance differed. While high doses led to anergy or deletion of antigen-specific T cells, repeated low-dose exposure led to induction of regulatory T cells and active suppression of immune responses to the antigen [12], although later reports have suggested that T regulatory cells can also be induced by oral administration of high antigen doses [13].

The quality of the tolerance induced might also vary by dose. In a murine model of food allergy, low-dose oral exposure to OVA and peanuts resulted in enhanced immune responses following immunisation with OVA or peanuts, while feeding high doses prior to immunisation led to the development of persistent antigen-specific oral tolerance [14]. The relevance of these findings to the development of oral tolerance or food allergy in humans is not yet known.

In murine models, exposure to food antigens through a damaged skin barrier can lead to the development of an immune response to these antigens and prevent subsequent induction of oral tolerance [15, 16]. It has been hypothesised that exposure to dietary antigens through the skin may also play a role in the development of food allergy in infants—termed the Dual Allergen Hypothesis [17]. One study suggested that environmental exposure to food allergens during infancy as a result of household consumption may increase the risk of food allergy. In the study by Fox et al., higher household peanut consumption was associated with an increased risk of peanut allergy in infants [18]. Interestingly, early oral exposure to peanuts in infants appeared to protect against the increased risk seen with higher household peanut consumption. There are as yet no confirmatory studies to support these results.

Treatment

- The current treatment for food allergy is avoidance of the offending food and prescription of appropriate medication for treatment of allergic reactions if they occur. For the prevention of food allergy, focus has recently shifted from allergen avoidance to active promotion of tolerance.

Allergen avoidance for the prevention of allergic disease

Allergen avoidance has long been a key focus in the primary (preventing development of disease), secondary (preventing disease progression) and tertiary (preventing symptoms in allergic individuals) prevention of allergic disease [19]. While allergen avoidance is still the mainstay for tertiary prevention of allergic disease including food allergy, its role in primary prevention is less clear. Historically, research has primarily targeted aeroallergen sensitisation and asthma, with food allergy only recently emerging as a research focus. Avoiding exposure to inhalant allergens such as house dust mites and pets was proposed as a strategy to reduce development of sensitisation to these allergens and

subsequent allergic disease; however, results of intervention studies have been conflicting and largely unsuccessful for primary prevention [19].

Similarly, the results of intervention studies of food allergen avoidance have failed to show a clear protective effect. Early trials of combined maternal and infant allergen avoidance appeared to reduce the likelihood of food allergy in infancy [20]; however, later follow-up of these cohorts found no evidence that any protective effect was maintained beyond the first few years of life [21]. This lack of protective effect of food allergen avoidance has been supported by several recent cohort studies reporting that delayed introduction of allergenic foods does not appear to be protective, and may even increase the risk of food allergy [22•, 23, 24, 25•]. Recently, interest has therefore turned towards active promotion of tolerance rather than allergen avoidance, with a review by Prescott et al. [26] suggesting that a critical “window of opportunity” exists for the introduction of solids in general and hypothesising based on rodent studies that this is likely to be between 4 and 6 months in humans.

Early food allergen exposure to promote tolerance

One of the first suggestions that early introduction of allergenic foods might be beneficial for food allergy prevention came from an ecological study comparing Israel and the UK, correlating early consumption of peanuts with a lower prevalence of peanut allergy in children in Israel [27]. However, the study design did not allow a direct link between age at first peanut consumption and peanut allergy on the individual level and was unable to eliminate other environmental factors as the cause of the between-country differences in prevalence of peanut allergy. This possibility is consistent with the study also finding a higher prevalence of other allergic conditions in the UK, in particular eczema which is closely associated with food allergy risk. Interestingly, there was a higher prevalence of egg and tree nut allergy in the UK, although this was not accompanied by a statistically significant difference in age at introduction of either of these foods at the population level.

Several observational cohort studies subsequently reported a lower risk of food allergy among infants introduced to allergenic foods early. Four cohorts provided evidence that timing of introduction of cow's milk [25•], wheat [23] and egg [22•, 24] might play a role in risk of allergy to those foods. However, causality cannot be determined from these studies as infant feeding practices are strongly influenced by factors that might confound the observed associations. While randomised controlled trials are therefore essential prior to making firm recommendations to introduce allergenic foods early, the collective evidence from existing observational studies suggests that early introduction is at the very least unlikely to increase the risk of food allergy, and may even protect against its development. It should, however, be noted that in these studies self-selection based on perceived risk of food allergy may have occurred. Thus, the highest-risk infants were probably not exposed to allergenic foods early, and information on risk of early introduction in these infants is therefore not available.

As well as timing of exposure, dose and type of allergen might be important. The Healthnuts study in Australia found that, compared with intro-

duction at 4–6 months, introducing egg into the diet later was associated with higher rates of egg allergy (adjusted odds ratio 3.4 [95 % CI 1.8–6.5] for introduction after 12 months) [22•]. Interestingly, introduction of cooked egg, such as scrambled, baked or fried, was more protective than simply introducing egg in baked goods (representing a lower dose of egg), with those introducing cooked egg at 4–6 months being five times less likely to develop egg allergy than those waiting to the normally recommended time of 10–12 months of age, even after adjusting for confounding factors. There was no protective effect amongst infants who first introduced baked egg into their diet between 4 and 6 months, suggesting a lower-dose exposure might not provide protection. Further studies that take into account dose and type of exposure are required to explore these issues.

Randomised controlled trials of early allergen exposure

The recent publication of results from the first randomised controlled trial of early introduction of egg for the prevention of egg allergy raises several important questions [28•]. In this study, of 77 infants with eczema randomised to either egg avoidance or introduction of egg powder from 4 months of age, 33 % in the egg group and 51 % in the control group were egg allergic at 12 months of age (relative risk 0.65, 95 % CI 0.38–1.11, $p=0.11$). Although this difference was not significant, there was some evidence that early introduction of egg modulated the immune response, with the early egg group showing persistently higher egg-specific IgG4 levels. Overall, the results suggested that early introduction of egg may prevent egg allergy in a proportion of infants predisposed to egg allergy development, although additional studies with greater power are required to confirm these findings. However, the study also raises some important questions that still need to be addressed. Although intended as a prevention trial, children with eczema and therefore at high risk of food allergy had high rates of sensitisation and allergy at 4 months prior to the introduction of egg, suggesting that this trial might have inadvertently been treating existing egg allergy rather than preventing development of egg allergy. The trial was also terminated early due to severe reactions in some children on initial ingestion of the egg powder, with reactions on first ingestion occurring in 31 % of infants, highlighting that this trial is likely to have selected for particularly high-risk infants.

Several additional intervention studies currently in progress have the potential to provide high-quality evidence about the role of infant feeding in food allergy as results become available over the next few years. Two studies are currently underway in the UK: the LEAP and EAT studies. The LEAP study aims to examine the effect of early peanut consumption on peanut allergy in children at high risk (defined as the presence of severe eczema or egg allergy) [29]. The EAT study aims to examine the effect of early consumption of a range of potentially allergenic foods on IgE-mediated allergy to any of these foods in a large population-based sample of infants [30]. The intervention arm of the EAT study will introduce six potentially allergenic foods (cow's milk, egg, wheat, sesame, fish and peanut) into the infants' diets from 3 months of age. The control arm will follow standard UK Government

advice of exclusive breastfeeding until 6 months of age and no introduction of allergenic foods—egg, wheat, peanuts, tree nuts, seeds, fish and shellfish—before 6 months.

Three further studies are also underway that aim to examine the early introduction of egg and involve the use of a placebo control: the HEAP study in Germany [31], and the STEP trial [32] and the BEAT study in Australia [33]. The HEAP study will involve 800 children, randomized to receive either hen's egg or a placebo at 4–6 months of age, with the effect on egg allergy measured at 12 months. The STEP trial will include 1,500 infants with atopic mothers. Infants will receive either whole egg powder or a placebo (rice powder) starting from 4 to 6.5 months of age up to age 10 months and challenge-proven egg allergy will be measured at age 12 months. The BEAT study ($n=600$ infants with a first-degree relative with atopy) involves introduction of freeze-dried egg powder with first weaning food (from 4 to 6 months) to 8 months compared with a placebo, with no dietary restrictions from age 8 months. Sensitisation and clinical reactivity to egg will be measured at 8 and 12 months of age.

Challenges with development and implementation of feeding guidelines at a population level

The accumulation of studies investigating the relationship between infant feeding and food allergy means that firm recommendations about the best time to introduce allergenic foods to infants might soon be possible. However, a number of challenges and unresolved issues remain that may hinder development and uptake of any revised guidelines at the population level.

Compliance with current and past infant feeding recommendations regarding optimal duration of exclusive breastfeeding, weaning and introduction of allergenic foods has often been suboptimal [34, 35]. In part, this may reflect confusion caused by the plethora of different infant feeding guidelines both within and between countries [8]. Failure to adequately disseminate information about the latest guidelines, the target audience for the guidelines, and the rationale and scientific basis of the recommendations may also be a contributing factor. As previously mentioned, other factors such as socioeconomic status and maternal country of birth are likely to contribute to responsiveness to modification of guidelines [10]. Perceived risk of an intervention is also likely to play a role, with parents with a history of allergic disease less likely to change behaviour towards early introduction of allergenic foods following the recent removal of advice to delay introduction of these foods [10].

Targeting infant feeding guidelines towards the appropriate group also poses potential issues. Past guidelines have sometimes targeted infants defined as 'high risk' (those with one or more allergic family members); however, the majority of the general population in developed countries such as Australia now meet this criteria [36]. It is currently not clear whether the relationship between infant feeding and food allergy differs depending on genetic risk profile, although there is evidence from the first randomised

controlled trial in eczematous infants that early introduction of egg may not be effective in preventing egg allergy in a subset of these infants, for reasons that are currently not known. Identifying those who will respond to early introduction may allow better targeting of guidelines.

Conclusions

Emerging evidence from a small number of observational cohort studies suggests that at a population level introduction of allergenic foods from 4 to 6 months of age is safe and may even be protective against the development of food allergy. The forthcoming completion of several randomised controlled trials has the potential to substantially improve knowledge in this area. Currently, more information is needed regarding safety of early introduction in high-risk infants, particularly those with severe eczema. Additionally, little evidence is currently available regarding the optimal timing and dose of various allergenic foods for prevention of food allergy. Future guidelines and advice regarding timing of introduction of solids will need to be contextualised within a wider framework of healthy infant development including promotion of breastfeeding, safety of food and water supply in developing countries, developmental readiness to start complementary foods and ensuring adequate supply of essential nutrients. Most importantly, systematic reviews of emerging literature will be critical to ensure appropriate assimilation of data to inform and update guidelines. Further work is needed to ensure that public health knowledge and attitudes to infant feeding guidelines remain receptive in a time of ongoing change in our evidence base.

Compliance with Ethics Guidelines

Conflict of Interest

Jennifer J. Koplin declares that she has no conflict of interest.

Katrina J. Allen received payment for lectures including service on speakers bureaus from Abbott, Wyeth and Nutricia.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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