

## **The importance of early complementary feeding in the development of oral tolerance: Concerns and controversies**

**Prescott SL, Smith P, Tang M, Palmer DJ, Sinn J, Huntley SJ, Cormack B, Heine RG, Gibson RA, Makrides M. The importance of early complementary feeding in the development of oral tolerance: Concerns and controversies.**

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Rising rates of food allergies in early childhood reflect increasing failure of early immune tolerance mechanisms. There is mounting concern that the current recommended practice of delaying complementary foods until 6 months of age may increase, rather than decrease, the risk of immune disorders. Tolerance to food allergens appears to be driven by regular, early exposure to these proteins during a “critical early window” of development. Although the timing of this window is not clear in humans, current evidence suggests that this is most likely to be between 4 and 6 months of life and that delayed exposure beyond this period may increase the risk of food allergy, coeliac disease and islet cell autoimmunity. There is also evidence that other factors such as favourable colonization and continued breastfeeding promote tolerance and have protective effects during this period when complementary feeding is initiated. This discussion paper explores the basis for concern over the current recommendation to delay complementary foods as an approach to preventing allergic disease. It will also examine the growing case for introducing complementary foods from around 4 months of age and maintaining breastfeeding during this early feeding period, for at least 6 months if possible.

There has been a clear and worrying increase in a diverse range of allergic and autoimmune diseases, which are all associated with an underlying failure of immune tolerance (to allergens and self-antigens). This emphasizes the need to understand the developmental origins of these conditions and, in particular, the role of early feeding practices in both pathogenesis and prevention.

In 2001, the World Health Organisation (WHO) revised its recommendation for exclusive breast feeding from 4 to 6 months. This was based (at least in part) on reduced gastrointestinal infectious disease noted in a Belarussian study and had major implications for disease burden in developing and semi-industrialized countries. At that time, there was also a paucity of evidence regarding the other risks and benefits of introducing complementary foods from 4 vs. 6 months of age. These recommendations were aimed at reducing morbidity in developing countries, but may not be appropriate in the growing world population experiencing progressive industrialization and escalating risk of immune dysregulation.

Similar recommendations have been adopted for the prevention of allergic disease in the USA, the UK, Australia and other industrialized countries, based on the theoretical concern for

increased gut permeability and immaturity of mucosal immunity in infants. However, there is now mounting concern and some new evidence that this recommendation for delayed introduction of complementary foods may have detrimental consequences. In Western countries, where these recommendations have been adopted into practice, rates of food allergy have escalated rather than declined in the last 10 yr (3-5). The purpose of this discussion paper is to highlight these concerns and controversies (in term infants), together with the rationale for revising guidelines to more accurately reflect current evidence, at least until more definitive studies can be performed.

### **Implication for immune tolerance**

Development of immune tolerance is a critical process in early life. The rising rates of allergic and autoimmune diseases highlight the susceptibility of these tolerance pathways to environmental changes. Although the mechanisms are not clear, many of these conditions (including food allergies, coeliac disease and type 1 diabetes) manifest early in life, indicating that immune dysregulation is a very early event. Animal models suggest that tolerance is an antigen (allergen)-driven process and that exposure to these proteins during a 'critical early window' of development may be essential to this process. This also appears to coincide with the establishment of healthy gut colonization, which has been shown to be essential in promoting tolerance to both allergens and self-antigens. Delays in either colonization or antigen / allergen exposure can lead to failure of oral tolerance. Conversely, allergen exposure too early when the gut colonization and local immune networks are less established may increase the risk of allergic or autoimmune disease (possibly through increased gut permeability). Some studies also suggest that continued breastfeeding during introduction of complementary foods is important for promoting tolerance. The timing of this 'critical window' for oral allergen exposure is not clear in humans, but current evidence suggests that this may be between 4 and 6 months of life, as discussed below. This raises further concerns over recommendations for delaying introductions of complementary foods until after 6 months of age, especially in industrialized countries where the incidence of allergy is high. It may be further argued that infants with a genetic predisposition to allergic disease (failure of oral tolerance) may require regular, larger 'doses' of food allergen to promote tolerance induction (as with immunotherapy). If this is the case, allergen avoidance is likely to be detrimental in these children. However, at this stage this is not known.

### **The basis and evolution of current recommendations for infant feeding in allergy prevention**

In the last 25 yrs., observational and primary allergy prevention studies in allergy with respect to the early introduction of complementary foods have been inconclusive, and at best, several studies demonstrate a transient increase in IgE, particularly to milk if foods were introduced before 3-4 months of age. Here, we explore the historical basis for current recommendations:

In the 1980s and 1990s, several studies reported an association between early introduction of solids (< 3-4 months) and eczema. This association did not persist beyond 12 months of age in two of these three cohorts. A number of subsequent prospective studies have failed to demonstrate an association between early introduction of complementary foods and either eczema or food allergy, and a recent systematic review concluded that there was 'no strong evidence to support the association between early solid feeding and the development of persistent asthma, persistent food allergy, allergic rhinitis, or animal dander allergy'.

Despite the paucity of clear evidence, conservative avoidance recommendations remain in place in many countries. These appear to be based on an early US study by Zeiger and Heller, which used combined dietary avoidance strategies in infants at risk of allergic disease.

Strategies included maternal allergen avoidance (in pregnancy and lactation), extensively hydrolysed formula if complementary feeding was required in the first year, and staged delay in introduction of solid foods: non-legume vegetables, rice cereal, meats and non-citrus fruits between 6 and 12 months; cow's milk, wheat, soy, corn and citrus fruits between 12 and 18 months; eggs at 24 months; and peanut and fish at 36 months. The main findings of these studies were as follows.

(i) Reduction in food-associated atopic dermatitis, urticaria and or gastrointestinal disease by 12 months (5.1 % vs. 16.4%;  $p = 0.007$ ). This was only significant with a grouped symptom analysis.

(ii) In the prophylaxis (treated) group, there was a lower rate of sensitization to foods at 24 months (16.5% vs. 29.4%;  $p = 0.019$ ), due mainly to fewer positive milk skin tests (1% vs. 12.4%;  $p = 0.001$ ).

(iii) Serum IgE levels in the prophylaxis group were marginally lower only at 4 months.

These findings could also be attributed to the use of an extensively hydrolysed formula. Despite this, the entire infant weaning structure of this study has been incorporated into the recommendations of the Committee on Nutrition of the American Academy of Pediatrics in 2000 and recently reinforced by a position paper from the American College of Asthma Allergy and Immunology. These avoidance recommendations have been presented at many international meetings and propagated by professional societies and government agencies to the wider community. The European Society for Paediatric Allergology and Clinical Immunology Committee on Hypoallergenic Formulas and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) have been more circumspect, suggesting the introduction of solids after 5 months.

In summary, the evidence for restricting infant diet (complementary foods) for up to 6 months is weak, comprising inconsistent findings of increased milk sensitization and eczema with complementary foods given in the first 3-4months.

## **Summary of current guidelines for allergy prevention**

In 2005, we (Prescott and Tang) revised the Australian allergy prevention guidelines, removing the inhalant avoidance strategies in light of weak evidence and paradoxical effects in some studies. We also raised concerns about the lack of good evidence to support many food allergen avoidance practices (some of which avoid 'allergenic' foods such as egg and peanuts for between 2 and 4 yr of age). As indicated above, any benefit of early food allergen avoidance appears to be largely in the first 3–4 months, with very little clear or consistent evidence that avoidance beyond this period reduces allergy risk. Therefore, in the context of allergy prevention, we elected to maintain the previous recommended duration of exclusive breastfeeding at '4–6 months' [consistent with the ESPGHAN recommendations of 5 months], despite the WHO recommendations for exclusive breastfeeding of all infants for 'at least 6 months'. Moreover, based on the current evidence (presented below), there may now be a case for revising this further to "4 months". Although the specific role in allergy prevention remains unclear, there is some evidence that continued breastfeeding while new foods are introduced is beneficial. When breastfeeding is not possible, the use of hydrolysed formulas appears to confer some protective effect compared with normal cow milk-based formulas and these are still recommended, although it is generally recognized that more studies are needed and the protective effects are not great. Thus, until more data are available, it is difficult to justify the restriction of complementary foods until 6 months of age, particularly in industrialized countries.

## **Rationale for reconsidering the role of early food allergen exposure**

The normal development of oral tolerance is an antigen-driven process and may logically depend on regular exposure to foods and other antigens during a critical early window. These processes are also likely to depend on other conducive exposures [such as favourable gut colonization, breast milk and/or other nutritional immunomodulatory factors]. It is now increasingly evident that allergen exposure is not the primary cause of the allergy epidemic, and that allergen avoidance may be unsuccessful, or even detrimental in allergy prevention. Indeed, although rising rates of immune disease are likely to reflect a combination of many environmental changes that compromise tolerance, the introduction of complementary foods must be considered in this complex modern context. Understanding other early host-environment interactions is essential to this.

## **Evidence to support a role of earlier exposure to food proteins in immune tolerance**

A number of recent studies suggest that exposure to specific foods in the 4–6 months age range may reduce the risk of food allergies and autoimmunity compared with children first exposed either before or after this 'window'.

Specifically, children initially exposed to cereals between ages 0 and 3 months [hazard ratio (HR), 4.32; 95% confidence interval (CI), 2.0- 9.35] and those who were exposed after 6 months (HR, 5.36; 95% CI, 2.08-13.8) had increased risk of islet cell autoantibodies than those who were exposed between 4 and 6 months. Similarly, delayed exposure to gluten (after 6 months) was associated with increased risk of coeliac disease autoimmunity (HR, 1.87; 95% CI, 0.97-3.60) and biopsy-diagnosed coeliac disease (HR, 3.98; 95% CI, 1.18-13.46;  $p = 0.04$ ) compared with those exposed at 4-6 months. Exposure prior to 4 months was also associated with increased risk of coeliac disease autoimmunity (HR, 5.17; 95% CL 1.44-18.57) and biopsy-diagnosed coeliac disease (HR. 22.97; 95% CI. 4.55-115.93;  $p = 0.001$ ).

Although early allergic disease outcomes are reduced in children who have not been exposed to complementary foods prior to 4 months, there is little evidence that avoidance beyond 4 months is beneficial. Moreover, avoidance beyond 6 months has been associated with increased risk of allergic disease (food allergy. eczema. asthma). One recent Australian study (in which reverse causation was excluded) showed that even delaying complementary foods until after 3 months was associated with an increased risk of atopy at 5 yr of age.

Intervention studies that have used infant dietary avoidance strategies for allergy prevention are difficult to interpret because most have used these in combination with other strategies such as hydrolysed formulas, maternal restrictions and/or other environmental interventions. Furthermore, dietary interventions also varied widely between studies (restricting 'any' complementary feeding for between 3 and 6 months and restricting specific solids such as egg, dairy, wheat, nuts, fish and soy up from between 4-12 months). Although some of these studies reported benefits on some allergic outcomes, the findings are not consistent and difficult to attribute specifically to infant dietary restrictions. Finally, in countries where early dietary restrictions (of complementary foods) have been adopted into practice such as the USA, the UK and Australia, rates of food allergy have escalated rather than declined.

### **New studies aimed at using early food allergen exposure to prevent allergy**

Challenging many long-held concepts, there are now studies (in progress and in design) that will examine the hypothesis that earlier introduction (rather than avoidance) and regular exposure to 'allergenic' foods (such as peanuts and egg) may reduce the risk of specific allergies to these foods.

There is currently a UK-based randomized controlled trial investigating the regular consumption vs. avoidance of peanut protein during infancy. This trial involves infants (4-11 months of age) with egg allergy, severe eczema or both. The intervention group is fed at least 6 g peanut protein weekly, distributed over at least three meals each week. The primary outcome of this study assesses the effects of this intervention on the proportion of children with peanut allergy at 5 yr of age. There is also a proposed Australian study that will examine the effects of early egg introduction in high-risk infants.

## **Other implications: growth, development and nutritional status**

The age when constituent breast milk consumption will no longer meet infant nutrition requirements is ill-defined. Current nutrient reference values (NRV) and energy requirements for the first 6 months are largely based on average intakes of healthy breastfed infants. Despite the rapid growth and development of infants during this period, many references ranges do not increase until 7 months when solid foods are currently recommended. Thus, NRV tend to be based more in feeding practice rather than physiological needs. A systematic review by Lanigan et al. showed a paucity of randomized trials and little evidence to support a change in recommended commencement of solids to 6 months.

There are concerns that delayed introduction of complementary feeding could compromise supply of nutrients essential for growth and neuro-development. Exclusive breastfeeding for 6 months has been associated with a higher risk of anaemia (10%) compared with breastfed infants receiving complementary feeding (2.3%). The WHO systematic review (31) also reported that infants exclusively breastfed to 6 months had a lower haemoglobin ( $p = 0.005$ ) and ferritin level ( $p = 0.04$ ) compared with those infants fed mixed breastfeeding at 4-6 months. Delayed complementary feeding may in some populations increase the risk of deficiencies of iodine, zinc and other specific micronutrients. This raises particular concerns that some infants may become deficient in essential micronutrients if solid foods are delayed. In addition to implications for growth, there are numerous other developmental issues surrounding the timing of dietary diversity, including the development of taste and food preferences, which also need to be addressed in this process.

## **Conclusions**

New studies that address the role of early exposure to allergenic foods (rather than avoidance) are greatly needed and awaited with utmost interest. However, until these studies have been completed, this issue is likely to remain unresolved. In the meantime, there is conflict between some allergy prevention guidelines that recommend introductions of complementary foods from '4 to 6 months' [e.g. as currently recommend in Australia] and the recommendation for exclusive breastfeeding until '6 months' [by the WHO and many other international government and professional bodies]. The evidence for delayed introduction of complementary foods to 6 months is very limited and difficult to justify in the face of emerging evidence that this may be detrimental. Rather, there is a growing case for further revising the recommended age for the introduction of complementary foods to '4 months' while breast feeding is maintained for at least 6 months where possible.