

# Prevention of food allergy in the real life

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## Summary

**The prevalence of food allergy has increased exponentially in the last decade and is fast becoming the second wave of the allergy epidemic. Secondary prevention methods such as treatment of accidental exposures and immunotherapy are still fraught with difficulties and unanticipated adverse events still occur. The future of food allergy management may lie in primary prevention, of which practical strategies and current evidence are summarized in this review. No maternal dietary restrictions are required during pregnancy and lactation. High risk infants should be exclusively breastfed for at least 4 to 6 months with early introduction of complementary solid foods. Hydrolyzed formulas may be used for high risk infants who are not exclusively breastfed. A healthy balanced diet inclusive of fresh fruits, vegetables and vitamins may play an important role in prevention of allergies and has myriad advantages to general health and well-being. There remains a need for large scale randomized controlled trials for all other nutritional interventions in the hope that more can be done for the primary prevention of allergies in the future. (*Asian Pac J Allergy Immunol* 2014;32:16-24)**

**Key words:** *food allergy, atopy, breastfeeding, complementary foods, hydrolyzed formula, probiotics, prevention*

## Introduction

Food allergy affects 3% to 10% of the world's population and its worldwide prevalence has increased significantly over the last two decades.<sup>1</sup> The prevalence of peanut and/or tree nut allergy in children in the UK and United States has more than doubled in the last 10 years.<sup>2,3</sup> The situation in Asia is no different, where the prevalence of food allergy in children lies between 3% to 8%.<sup>4</sup> There is a concern that food allergy is now the second wave of the allergy epidemic, after asthma.<sup>5</sup>

The management of food allergy is rapidly evolving. In the past, the cornerstone of conventional food allergy management was allergen avoidance and emergent treatment of accidental exposures. In recent years, oral immunotherapy has emerged as a ray of hope for all food allergy sufferers as a means towards achieving eventual tolerance. However this has been tempered by risks of severe adverse reactions and lack of definitive evidence of long-term efficacy. Thus there remains a pressing need for large scale prospective clinical trials to assess its safety and efficacy for everyday clinical practice.<sup>6</sup>

The focus has now shifted towards prevention as a strategy to bring the "allergy epidemic" to a halt. By implementing immunomodulation from an early age or even in-utero, prevention of sensitization might translate to a lower risk of developing allergies. Twin<sup>7</sup> and family studies<sup>8</sup> indicate evidence for a heritable component in food allergy, however genome wide association studies (GWAS) have not yet been able to identify specific candidate genes for food allergy that may be targeted for new therapeutic approaches in the future.<sup>9</sup> The complex interactions between epigenetics and the environment may play key roles in modulating sensitization in infancy and the development of allergic diseases,<sup>9</sup> thus modification of such environmental factors in early life may be the first step in the prevention of food allergies.

Prevention strategies that have been proposed include dietary modification during pregnancy and lactation, breastfeeding and its alternatives, timing of introduction of complementary foods as well as

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the addition of micronutrients and immune-modulatory supplements such as probiotics, vitamins, fatty acids and antioxidants. This review summarizes the existing evidence in the literature, recent revisions to expert recommendations and guidelines and discusses interventions for the future.

### **Maternal Dietary Restriction in Pregnancy**

The American Academy of Pediatrics (AAP) guidelines on nutrition which were released in 2000 recommended that mothers of infants at high risk of atopy should eliminate highly allergenic foods such as peanuts and tree nuts from their antenatal diets, and consider elimination of eggs, cow's milk, fish and other foods while nursing.<sup>10</sup> However, evidence has since shown that maternal allergen avoidance has in fact no effect on prevention of atopy in infants. Kramer and Kakuma's Cochrane review in 2012<sup>11</sup> on a meta-analysis of four trials did not find a protective effect of maternal antigen avoidance on the incidence of atopy in children. On the contrary, the restricted diet could conversely have a detrimental effect on maternal and fetal nutrition. The Danish National Birth Cohort examined associations between maternal peanut intake during pregnancy and the development of allergy in children. Their 7-year outcomes found that children of mothers who reported regular consumption of peanuts and tree nuts during pregnancy had a lower risk of developing asthma (peanuts OR 0.79, 95% CI 0.65 – 0.97; treenuts OR 0.75, 95% CI 0.67 – 0.84), compared to children of mothers on nut-free diets. In the light of the new evidence, the NIAID (National Institute of Allergy and Infectious Diseases) as well as the AAP revised their guidelines in 2008 to state that no dietary restrictions are necessary during pregnancy or lactation for the prevention of allergic diseases in the infant.<sup>12,13</sup>

### **Exclusive Breastfeeding**

Breast milk is widely acknowledged as the optimum source of nutrition for all infants. Its unique composition of protein, fat, water, minerals and immunological properties as well as its ability to change according to the infant's age and needs are far superior to any commercial formula. Research has demonstrated a decreased risk of infections, sudden infant death syndrome (SIDS), obesity, autoimmune diseases such as celiac disease, inflammatory bowel disease and Type 1 diabetes mellitus and better neurodevelopmental outcomes in breastfed infants.<sup>14</sup> Lactating mothers also enjoy

extended medical, metabolic, economic and psychosocial advantages by breastfeeding for at least 4 months.

There is evidence that breastfeeding reduces the risk of atopic dermatitis especially in high risk infants who have a family history of atopy. Gdalevich's meta-analysis of 18 prospective studies evaluated the association between exclusive breastfeeding during the first 3 months of life and atopic dermatitis.<sup>15</sup> They found that infants who were exclusively breastfed for 3 months had a lower incidence of atopic dermatitis (OR 0.68, CI 0.52-0.88). This association was strengthened in high risk infants with a familial predisposition (OR 0.58, CI 0.41-0.92). The German Infant Nutritional Intervention Program (GINI) observed a similar reduced risk of atopic dermatitis in high risk infants who were exclusively breastfed for 4 months, as compared to those who received supplemental cow's milk formula.<sup>16-18</sup>

The evidence for non-high risk infants for prolonged breastfeeding is weaker. The GINI program observed no difference in the incidence of atopic dermatitis between non-high risk infants receiving exclusive breast milk, cow's milk or hydrolyzed formula.<sup>16</sup> Other more recent studies including that by Yang et al.<sup>19</sup> and the European ISAAC (International Study of Asthma and Allergies in Childhood) study both did not find any evidence that exclusive breastfeeding beyond 4 months was protective against eczema. Some proposed that there was in fact a positive association between the duration of breastfeeding and atopic dermatitis.<sup>20</sup> The counter-argument is, however, that statistical methods cannot account for reverse causation whereby mothers of infants who develop early onset eczema may intentionally prolong breastfeeding because of its known immunomodulatory benefits.

Thus, the AAP now recommends that high risk infants should be exclusively breastfed for at least 4 to 6 months, but there is insufficient evidence that this protection extends beyond 6 months.<sup>13</sup>

### **Breast milk alternatives**

Breast milk is best. But there are mothers who are unable, or choose not, to breastfeed for at least 4 months. They then have the dilemma of choosing between the multitudes of breast milk alternatives available in the market. The GINI trial showed a protective effect of hydrolyzed cow's milk over standard cow's milk formula on the cumulative



incidence of allergic disease, especially atopic dermatitis<sup>21</sup>. There was evidence for a slight advantage of extensively hydrolyzed casein (OR 0.83, 95% CI 0.72-0.95) over partially (OR 0.87, 95% CI 0.77-0.99) and extensively hydrolyzed (OR 0.94, 95% CI 0.83-1.07) whey formula.

The NIAID guidelines in 2010 thus recommended that in the absence of exclusive breastfeeding, extensively hydrolyzed casein infant formulas should be considered over standard cow's milk formulas for the prevention of food allergy in at-risk infants.<sup>22</sup>

Soy protein-based formulas have not shown any protective effects on the development of allergy in high-risk infants<sup>23, 24</sup> and are not recommended for the prevention of atopy.<sup>22</sup>

### Timing of introduction and choice of complementary foods

The 2000 AAP guidelines recommended that exclusive breastfeeding, with the exclusion of cow's milk formulas and supplementary foods, was indicated during the first 6 months of life to prevent the onset of allergic diseases later in life. Delaying exposure to solid foods until after 6 months was thought to be likewise protective. It was even recommended that cow's milk protein be withheld until after 12 months, "highly allergenic" foods such as eggs introduced at 2 years and peanuts, tree nuts and fish only after 3 years of age.<sup>25,26</sup>

Since then, research suggests that the converse is however true. Katz et al.'s large scale population based study found that early exposure to cow's milk protein was protective against the development of IgE-mediated cow's milk protein allergy.<sup>27</sup> (Table 1) In the Australian "HealthNuts" study, infants introduced to eggs later in life had a significantly higher risk of egg allergy than those who were exposed very early between 4 to 6 months of age. This risk increased with older age at first egg exposure: OR 1.3 (95% CI 0.8 – 2.1) at 7 to 9 months of age; to OR 3.4 (95% CI 1.8 – 6.5) if introduced after 12 months.<sup>28</sup> A Finnish study demonstrated that early introduction of cereals, fish and eggs was associated with decreased atopic sensitization and a lack of dietary diversity at 3 months of age in fact translated to a greater likelihood of food sensitization. These results were also more significant among high-risk infants.<sup>29</sup>

One wonders if the concept of reverse causality might again be responsible for this new phenomenon: in that parents of infants showing

signs of eczema in early infancy, cognizant of previous food allergy guidelines, might delay the introduction of solids in an attempt to prevent their children from developing food allergies. Sariachvili et al.<sup>30</sup> attempted to address this through a nested case-control study examining weaning practices in association with atopic dermatitis, in which early exposure to solid food was defined as introduction during the first 4 months before the occurrence of eczema. They too came to the same conclusion that early introduction of solid foods within the first 4 months was inversely associated with eczema up to 4 years of age (OR 0.49, 95% CI 0.32-0.74).

In the wake of these new findings, the NIAID<sup>22</sup> and AAP<sup>13</sup> released new guidelines in 2008 recommending that the introduction of solid foods should not be delayed beyond 4 to 6 months of age and potentially allergenic foods may be introduced at this time as well but in a sensible fashion. After 4 to 6 months of age, there is no convincing evidence to suggest a protective effect of any dietary intervention for the development of allergic diseases.

### Micronutrients and other supplements

The gut mucosa hosts a rich milieu of cytokines, micro-organisms, antibodies and regulatory T cells. Exposure to food proteins in early life modulates these complex immunological interactions, through which induction of tolerance results. Many strategies have been employed to alter the gut flora via the administration of living micro-organisms such as probiotics, as well as potentially immunomodulatory substances such as vitamins, long chain polyunsaturated fatty acids and folic acid, in an attempt to alter immune tolerance.

#### Probiotics

A large randomized controlled trial by Kukkonen et al.<sup>31</sup> examined the role of pro- and prebiotics in the prevention of allergic disease in high risk infants, beginning with antenatal administration and continuing through the first 6 months of life. Their findings suggested that probiotic treatment had no effect on the cumulative incidence of allergic diseases by 2 years of age but significantly reduced the incidence of atopic eczema (OR 0.66, 95% CI 0.46-0.95, relative risk reduction 34%). A meta-analysis by Pelucchi et al. observed a similar protective effect of probiotics on the incidence of eczema (RR 0.79, 95% CI 0.71-0.88).<sup>32</sup>

Other authors, however, did not concur. Taylor et al.<sup>33</sup> did not find a significant difference in



**Table 1.** Timing of introduction of complementary foods and development of food allergies

Study	Food type	Age of introduction	Odds ratio	95% Confidence Interval	P value	
Katz et al. <sup>27</sup>	Cow's milk	<14 days	1.00			
		15-194 days	19.3	6.00 – 62.1	<0.001	
Koplin et al. <sup>28</sup> (HealthNuts)	Egg	4-6 months	1.00			
		7 – 9 months	1.4	0.9 – 2.1		
		10 – 12 months	1.6	1.0 – 2.6		
		>12 months	3.4	1.8 – 6.5	<0.001	
Nwaru et al. <sup>29</sup>	Oats	<5 months	1.00			
		5.6 – 5.5 months	0.85	0.48 – 1.52		
		> 5.5 months	1.82	0.99 – 3.37	0.002	
	Rye	<5.6 months	1.00			
		5.6 – 7 months	1.23	0.74 – 2.03		
		> 7 months	2.30	1.40 – 3.75	0.002	
	Fish	< 6.1 months	1.00			
		6.1 – 8.2 months	1.50	0.89 – 2.53		
		>8.2 months	2.42	1.48 – 3.95	0.002	
	Eggs	< 8.1 months	1.00			
		8.1 – 10.5 months	1.04	0.60 – 1.80		
		>10.5 months	2.02	1.23 – 3.32	0.002	

eczema between infants receiving *Lactobacillus acidophilus* or placebo. Rather, they observed a higher proportion of food sensitization in the intervention group.

Given that the apparent protective effects of probiotics conferred upon infants with atopic dermatitis did not translate to a corresponding reduction in food sensitization or eventual clinical allergy and the contradictory conclusions between other large studies, the evidence remains unconvincing for a definite recommendation for the use of probiotics for allergy prevention.

#### **Long chain polyunsaturated fatty acids**

Dietary long chain polyunsaturated fatty acids (LCPUFA) are known to have immunomodulatory effects. Omega-6 LCPUFAs increase prostaglandin E2 (PGE2) production, favouring IL-1 and IL-6 pro-inflammatory responses and Th-2 differentiation. Omega-3 LCPUFAs inhibit PGE2, thus dampening Th-2 differentiation and the development of allergic inflammation. In recent years, “westernized” diets have resulted in a shift towards an increase in omega-6 and an inversely proportionate reduction in desirable omega-3 fatty acid intake, propagating dysregulation of the essential omega-3/omega-6 fatty acid balance. Some have proposed that this imbalance might be a contributory factor to the exponential increase in allergic diseases over the last two decades.

Furuhjelm et al.<sup>34</sup> reported a lower incidence of IgE associated allergic disease persisting until 2

years in infants whose mothers received omega-3 LCPUFA supplementation during pregnancy and first 3.5 months of lactation. The DOMInO (Docosahexaenoic Acid to Optimise Mother Infant Outcome) trial by Palmer et al.<sup>35</sup> found that fish oil supplementation during pregnancy alone initially resulted in a lower risk of atopic eczema (adjusted RR 0.64, 95% CI 0.40-1.02) and egg sensitization (adjusted RR 0.62, 95% CI 0.41-0.93) in the first year of life. However, there was no reduction in the overall incidence of IgE-mediated allergies and their subsequent follow up study<sup>36</sup> showed that the initial protective effect did not persist to 3 years of age.

A meta-analysis<sup>37</sup> also indicated evidence to the contrary, lending credence to the recommendation that omega-3 and omega-6 oils were not likely to be useful in the primary prevention of sensitization or allergic disease.

#### **Vitamins / Folate**

Data is conflicting on Vitamin D supplementation for the prevention of allergies. Excessive Vitamin D shifts the cytokine profile towards Th-2 predominance, predisposing to allergic inflammation.<sup>38</sup> Studies in the United States<sup>39</sup> and Finland<sup>40</sup> found an increased association between Vitamin D supplementation in infancy and the development of atopy in later life. However limitations in these studies include methodology issues (inclusion of only exclusively formula fed black children in the US study) and high drop-out rates in the Finnish birth cohort study in which only

half of the initial birth cohort were eventually analyzed for atopy, thus this data must be interpreted with caution.

Others argue that Vitamin D is essential for downregulation of inflammatory mediators, suppression of Th-17 and maintaining the Th-1/Th-2 balance, thus a Vitamin D deficient state sets the stage for an increased risk of allergen sensitization and allergic asthma.<sup>41</sup> Vassallo et al.<sup>42</sup> and Camargo et al.<sup>43</sup> suggested that lack of sunlight exposure in northern latitudes especially during seasonal variations, which is essential for Vitamin D synthesis<sup>42</sup>, was associated with an increased risk of allergies, lending support to the Vitamin D deficiency hypothesis.

The current evidence on Vitamin D supplementation remains controversial and long term interventional studies are still needed to determine a clear association with atopy and to determine if there is a dose-dependent effect.

The few studies on folate supplementation are also conflicting. Matsui observed an inverse relationship between serum folate levels in children and their serum IgE and presence of atopy and wheeze<sup>44</sup>, suggesting a protective effect of folate supplementation. However, a Dutch study suggested that high maternal antenatal folate levels were associated with an increased prevalence of atopic dermatitis in infants.<sup>45</sup> Until large scale randomized controlled trials are carried out, no definite recommendations can be made on folate supplementation for allergy prevention at this time.

### **The “Healthy Diet”**

Modern dietary changes have had farther reaching implications than were previously known. Consumption of higher proportions of omega-6 LCPUFAs and decreasing intake of healthy alternatives such as fresh fruits and vegetables, in tandem with increasingly sedentary lifestyles, have culminated in upward spiraling rates of obesity worldwide. High body mass index (BMI) correlates with a chronic inflammatory state, resulting in upregulation of pro-inflammatory cytokines such as TNF, IL-2, IFN $\gamma$ , IL-17<sup>46,47</sup> and C-reactive protein, a marker of systemic inflammation.<sup>48</sup> Childhood obesity is also well known to be positively associated with asthma<sup>49</sup>, in particular the severe, difficult to treat phenotype.<sup>50</sup>

The Mediterranean diet has been proposed as a healthy alternative to the undesirable “Westernized” diets of today. Advocates recommend a return to a more traditional culinary lifestyle of higher

proportions of olive oil, legumes, unrefined cereals, fruits, and vegetables, moderate to high consumption of fish, dairy products and wine and low consumption of meat and meat products. This diet, being low in saturated fat and high in monounsaturated fat, fibre and antioxidants, is thought to sustain not only a lower inflammatory metabolic profile but also confers cardiovascular and neuro-protective effects as well as a reduction in oncological risks.<sup>51</sup> Another large-scale meta-analysis of 62 studies by Nurmatov et al.<sup>52</sup> likewise found that the consumption of vitamins A, D, E, zinc, fresh fruit, vegetables and Mediterranean diet was protective for persistent wheeze (OR 0.22, 95% CI 0.08 – 0.58) and atopy (OR 0.55, 95% CI 0.31 – 0.97). However none of these studies were randomized controlled trials.

Grimshaw et al.’s nested case-control study found that infant diets consisting of high levels of fruits, vegetables, and home-prepared foods was associated with less food allergy by the age of 2 years. A negative association was observed with the consumption of highly processed adult and commercial baby foods more than once a day.<sup>53</sup>

Evidence suggests a strong indication for consumption of a healthy diet rich in fruits, vegetables and low in saturated fat and processed foods for its beneficial associations with asthma and food allergy outcomes, in addition to its known advantages to general health and well-being.

### **Newer interventions for the future**

Research into newer interventions for the prevention of allergy holds great promise. A large scale cohort study by Flohr et al.<sup>54</sup> showed that severity of atopic dermatitis even at 3 months of age was positively associated with an increased risk of food sensitization. Future advances in avoiding food allergies in children with atopic dermatitis could be directed towards attempting to reduce food sensitization through aggressive, proactive skin care for better eczema control.

A retrospective study by Fukuie et al.<sup>55</sup> observed that both total IgE and food specific IgE levels were significantly reduced in patients with atopic dermatitis who underwent proactive topical corticosteroid treatment on top of usual skin care regimens. However, prospective interventional studies that showed a reduction in atopic dermatitis through administration of probiotics were unable to demonstrate a similar reduction in food sensitization.<sup>56,57</sup>



A large population based cohort study by Koplin et al.<sup>58</sup> found that risk factors increasing infant microbial exposures in the first year of life, such as an elder sibling attending daycare as well as household pets, were associated with a lower risk of developing food allergies. More studies into targeted environmental microbial exposure in infancy would be useful to determine if this might be truly the way forward in prevention of food allergies.

The role of allergen introduction in the neonatal period or very early infancy as primary prevention for food allergy is unknown. Katz et al.<sup>27</sup> observed a significant reduction in IgE mediated cow's milk allergy in infants who were exposed to cow's milk protein as early as 14 days of life. There are very few studies that have examined such a relationship between complementary food exposures before 4 months of age and the development of food allergies later in life.

Other exciting developments include prophylactic mRNA vaccinations against specific allergens. These have been studied in mouse models which demonstrated an immune deviation towards a Th1 phenotypes and reductions in specific IgE, hence "immunizing" against type I allergies.<sup>59</sup>

These novel interventions, albeit currently backed by underpowered studies, may eventually form the new frontiers of allergy prevention in the future. Robust, well-designed randomized controlled trials in these areas are needed to form a convincing evidence base for firm recommendations.

## Practical recommendations

Faced with much evidence, many of which are conflicting or contradictory, and guidelines which appear to change abruptly within the space of a few short years, physicians struggle to keep up with up to date knowledge with which to empower their patients. Recommendations which are straightforward and practical for ease of recollection and implementation for both physician and patient alike are much desired. Table 2 summarizes the current evidence for high risk and non-high risk infants for the prevention of allergies.

Exclusive breastfeeding for at least 4 months is protective, after which complementary foods may be introduced in tandem with continued breastfeeding between 4 to 6 months of age. No dietary interventions beyond 6 months of age have been proven to be protective. Hydrolyzed formulas may be used for high risk infants who are not exclusively breastfed. No maternal or any other infant dietary restrictions, including that of allergenic foods, are recommended. A healthy balanced diet inclusive of fresh fruits, vegetables and vitamins is beneficial for overall health and there may be a role in prevention of allergies as well. There remains a need for large scale randomized controlled trials for all other nutritional interventions in the hope that more can be done for the primary prevention of allergies in the future.

**Table 2.** Summary of recommendations

	All infants (non high risk)	High risk infants
Maternal diet (antenatal and lactation)	<ul style="list-style-type: none"> <li>• Healthy balanced diet including all major allergens</li> <li>• No maternal dietary restrictions</li> </ul>	<ul style="list-style-type: none"> <li>• Healthy balanced diet including all major allergens</li> <li>• No maternal dietary restrictions</li> </ul>
Breastfeeding	<ul style="list-style-type: none"> <li>• Exclusive breastfeeding for the first 4-6 months</li> </ul>	<ul style="list-style-type: none"> <li>• Exclusive breastfeeding for the first 4-6 months</li> </ul>
Alternative Formulas	No specific guidelines	<ul style="list-style-type: none"> <li>• Partially or extensively hydrolyzed formula for the first 6 months if unable to exclusively breastfeed</li> <li>• Soy milk is not protective</li> </ul>
Complementary food introduction	<ul style="list-style-type: none"> <li>• Begin at 4-6 months</li> <li>• Start with sensible introduction of foods such as: first stage well pureed baby rice cereals, fruits and vegetables</li> <li>• Progress to soft or mashed meat, pasta and other second stage foods as appropriate</li> <li>• No avoidance of allergenic foods required</li> </ul>	<ul style="list-style-type: none"> <li>• Begin at 4-6 months</li> <li>• Start with sensible introduction of foods such as: first stage well pureed baby rice cereals, fruits and vegetables</li> <li>• Progress to soft or mashed meat, pasta and other second stage foods as appropriate</li> <li>• No avoidance of allergenic foods required</li> </ul>
Highly allergenic foods	Gradual introduction of egg, dairy, peanuts, tree nuts, fish and shellfish once able to tolerate less allergenic foods	Common sense introduction: <ul style="list-style-type: none"> <li>• One food at a time, beginning with a small amount</li> <li>• No more than one new allergenic food should be introduced at a time</li> </ul>
Micronutrients	No specific guidelines	Healthy balanced diet (Mediterranean diet)



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