Abstract
Due to the recent exponential increase in food allergies and atopic disorders, effective allergy prevention has become a public health priority in many developed regions. Important preventive strategies include the promotion of breastfeeding and vaginal deliveries, judicious use of perinatal antibiotics, as well as the avoidance of maternal tobacco smoking. Breastfeeding for at least 6 months and introduction of complementary solids from 4–6 months are generally recommended. Complex oligosaccharides in breast milk support the establishment of bifidobacteria in the neonatal gut which stimulate regulatory T lymphocyte responses and enhance tolerance development. Maternal elimination diets during pregnancy or lactation are not effective in preventing allergies. If exclusive breastfeeding is not possible, (supplemental) feeding with a partially hydrolyzed whey-based formula or extensively hydrolyzed casein-based formula may reduce the risk of cow’s milk allergy and atopic dermatitis in infants with a family history of atopy. By contrast, asthma and allergic rhinitis at 4–6 years of age are not prevented by this approach. Soy formula and amino acid-based formula have no proven role in allergy prevention. Perinatal supplementation with probiotics and/or prebiotics may reduce the risk of atopic dermatitis, but no reliable effect on the prevention of food allergy or respiratory allergies has so far been found. A randomized trial on maternal fish oil supplementation during pregnancy found that atopic dermatitis and egg sensitization in the first year of life were significantly reduced, but no preventive effect for food allergies was demonstrated. The role of vitamin D deficiency or excess as a risk factor for food allergy and atopic disorders requires further study.
**Introduction**

Over the past two decades, the prevalence of allergic disorders has increased exponentially [1]. This trend has mainly affected Western societies but is now also evident in emerging economies in the Asia-Pacific region [2, 3]. The greatest increase in allergic disorders has involved food allergy and atopic eczema in infants and young children, whereas the incidences of asthma and respiratory allergies appear to have stabilized. From 1995 to 2005, hospital admissions in Australia for food anaphylaxis have increased by about 350% [4], and the rate of challenge-proven food allergy has risen to more than 10% in 1-year-old children (peanut 3.0%, egg 8.9%) [5]. In view of this recent sharp increase in allergic disorders, effective allergy prevention strategies have become a major public health priority. Primary allergy prevention seeks to minimize the risk of allergic sensitization to foods and environmental allergens. Several approaches to allergy prevention have been developed (table 1). Strategies range from attempts to modify exposures to pollutants (e.g. tobacco smoke), dietary measures (e.g. promotion of breastfeeding) or modification of microbial exposures (e.g. reduced use of perinatal antibiotics).

The recent surge in allergic diseases has coincided with improved sanitation and a reduction in infectious diseases (‘hygiene hypothesis’). However, the etiology of allergic disorders is not completely understood. While genetic risk factors for allergic disease are well recognized (e.g. filaggrin gene defects in atopic dermatitis [6], thymic stromal lymphopoietin polymorphisms in asthma [7] or eosinophilic esophagitis [8]), these alone cannot explain the recent increase in allergic diseases. It appears more likely that environmental factors associated with a ‘Western lifestyle’ (e.g. environmental pollutants, microbial burden and dietary factors) modify genetic allergic risk and gene expression. The role of epigenetic imprinting in this process has been highlighted [9, 10]. Tobacco smoking is another well-recognized factor that stimulates T helper 2 lymphocyte responses and increases the allergic risk in young infants [11]. Avoidance of maternal tobacco smoking during pregnancy and lactation is therefore a key strategy in minimizing allergy risk.

**Early Gut Colonization, Microbial Biodiversity and Allergy Risk**

During early infancy and childhood, the fecal microbiome undergoes important developmental changes. These changes are thought to impact significantly on the maturation of immune responses and on tolerance development. The sterile and initially aerobic gut environment of the neonate is first colonized by facultative bacteria, including *Escherichia coli*, *Enterococcus* spp. and *Staphylococcus* spp.
Complex oligosaccharides in breast milk provide the substrate which promotes the establishment of anaerobic bacteria, including *Bifidobacterium*, *Bacteroides* and *Clostridium* spp. Bifidobacteria are thought to be crucial in promoting mucosal tolerance via the stimulation of innate immune responses (Toll-like receptors) and induction of regulatory T lymphocyte responses [14, 15]. The mode of delivery affects the composition of the fecal microbiota in the newborn period. In infants born via Caesarean section, the gut microbiota reflect the maternal skin flora, including Staphylococci, rather than vaginal flora that predominates in infants born via vaginal tract delivery [16]. The differences in early gut colonization between vaginally and surgically delivered infants have profound effects on early tolerance development. It is therefore not surprising that infants born via Caesarean section have a higher risk of allergic disease and asthma [17, 18]. By contrast, term infants who were born vaginally and were breastfed exclusively seem to have the most 'beneficial' gut microbiota (highest numbers of bifidobacteria and lowest numbers of *Clostridium difficile* and *E. coli*) [19].

**Strategies to Promote Fecal Microbial Biodiversity**

Gut microbiota and environmental microbial burden play a central role in early immune development and are likely to influence immunological events that lead to allergy. For example, growing up in a rural farm environment has been shown to significantly reduce the risk of asthma and allergic disease in children [10, 20]. There are significant differences in the gut microbiota profiles between allergic and nonallergic infants and children. Allergy and asthma risk are inversely associated with the degree of microbial biodiversity [21, 22]. Infants with IgE-associated eczema have significantly reduced fecal microbial diversity in the first month of life, compared to nonatopic infants [23, 24]. Modification of early gut colonization and fecal microbial diversity in infancy may thus provide an avenue for preventive or therapeutic strategies. Possible ways to establish a tolerogenic gut milieu in early infancy include the promotion of natural vaginal deliveries, exclusive breastfeeding for at least 6 months, judicious use of perinatal antibiotic-
ics and living in a farm environment (table 2). Probiotic or prebiotic supplementation has also been shown to modify the risk of allergies, particularly for atopic dermatitis in infancy [25, 26].

**Dietary Allergy Prevention**

Breastfeeding is one of the main pillars in allergy prevention [27–31]. Breast milk provides the most appropriate source of nutrition for the young infant as it contains a species-specific mixture of nutrients, growth factors and protective maternal antibodies. The World Health Organization (WHO) recommends exclusive breastfeeding for at least 6 months, taking into consideration not only allergy prevention but also general nutritional aspects, including prevention of respiratory and gastrointestinal infection. Breastfeeding is associated with the establishment of fecal microbiota high in bifidobacteria [32]. Bifidobacteria are thought to promote mucosal tolerance interact via regulatory T lymphocytes and Toll-like receptors [14]. The duration of exclusive breastfeeding appears to influence the risk of allergic disease [33, 34]. The protective effect of breastfeeding on eczema in the first 2 years of life appears to be modified by maternal allergy status [35]. Several studies have found no evidence that exclusive breastfeeding for 6 months or more prevented asthma, eczema or atopy at 5 years of age [31, 36]. In addition, a recent large longitudinal study showed that exclusive breastfeeding for at least 3 months was associated with a protective effect against infantile eczema, asthma and food allergies at 7 years of age, but a paradoxically increased asthma risk later in life [37].

**Hydrolyzed Formulas**

Partially hydrolyzed formula (PHF) has been recommended for allergy prevention in infants with a family history [30]. This recommendation follows the Cochrane review on the role of hydrolyzed formula in allergy prevention which
found a limited beneficial effect (compared to cow’s milk formula; CMF) in infants with a family history of atopy [38]. The German Infant Nutritional Intervention (GINI) study [39], to date the largest quasi-randomized trial comparing the effects of PHF, extensively hydrolyzed formula (EHF) and CMF, has provided the most convincing data for a protective effect for PHF and EHF. However, other studies have found no significant preventive effect for PHF [40]. The GINI study demonstrated a sustained preventive effect against atopic eczema until the age of 6 years after use of whey-based PHF or casein-based EHF, but no effect on respiratory allergies and asthma. A meta-analysis has confirmed a treatment benefit for PHF in infants with atopic dermatitis [41]. Health economic modeling found this approach cost-effective in a range of health care settings [42–44]. Others have questioned the role PHF and cautioned against overstating the preventive effect for allergic disease [40, 45]. In summary, hydrolyzed formulas may prevent atopic dermatitis in high-risk infants, but respiratory allergies are not prevented.

Soy Formula

In past years, there has been a growing concern about the safety of exclusive soy feeding in infants under 6 months, as reflected in a position paper by the European Society for Pediatric Gastroenterology and Nutrition [46]. A Cochrane review based on three randomized clinical trials showed no significant preventive effect of soy formula on the development of allergic disease [47]. Although soy formula may have a role in the treatment of cow’s milk allergy (CMA), as well as conditions such as lactose intolerance or galactosemia, its use for the purpose of allergy prevention in infants less than 6 months of age is currently not recommended [48].

Amino Acid-Based Formula

Amino acid-based formula (AAF) has been shown to be effective and nutritionally complete in the treatment of infants with CMA [49]. Its preventive effects on food allergy or atopic disorders, however, have never been assessed [28]. This is mainly because the cost of the formula prohibits its widespread use in allergy prevention. In theory, AAF may also have disadvantages in immune maturation of the young infants, as oral tolerance development is believed to be an active regulatory process that requires the stimulation of the infant’s gut-associated immune system by ingested antigens [50]. The use of AAF for primary allergy prevention is not recommended.
Timing of the Introduction of Weaning Foods

Fergusson et al. [51] were among the first to demonstrate an increase in risk of atopic dermatitis if weaning solids were introduced before 4 months of age. A large German birth cohort study [52], however, found no protective effect of the delayed introduction (after 4 months) of solids on atopic dermatitis at 4 years of age. Previously, the delayed introduction of common food allergens (cow’s milk after 12 months, egg after 2 years and peanut after 3 years) was recommended in an attempt to prevent food allergy [53]. However, more recently there has been a shift away from prolonged avoidance to earlier dietary introduction [54]. Findings from several small studies provide support for the concept of a ‘window period’ for tolerance induction, whereby tolerance is more likely to be achieved if weaning solids are introduced between 4 and 6 months of age. This reflects the feeding practices in many European countries but is not supported by the current WHO guidelines. Several prospective studies are currently underway to assess the effect of the early complementary diet on allergy risk. Until these studies are available, it will be difficult to make meaningful recommendations regarding the best timing of a complementary diet.

Maternal Elimination Diets during Pregnancy and Lactation

Exposure of the infants to intact food allergens that are secreted into breast milk can be reduced by maternal dietary avoidance [55]. It appeared therefore plausible that modification of diet during pregnancy and lactation may modify allergy risk. The Isle of Wight prevention study [56] examined the effect of breastfeeding (while mothers maintained an allergen-reduced elimination diet), complementary feeding with EHF and concurrent house dust mite avoidance on the development of food allergy and atopy. Although at 2 years the rate of food allergy in the active intervention group was lower, this difference was lost on repeated measurement analysis at 8 years of age. The Cochrane review found no significant primary preventive effect of maternal elimination diets for allergic diseases but warns against possible adverse nutritional outcomes for mother and infant [57]. Maternal elimination diets during lactation may reduce the severity of established eczema (secondary and tertiary prevention). However, maternal elimination diets during pregnancy for the purpose of primary allergy prevention are not deemed effective.
**Probiotics and Prebiotics**

Infants with allergies have been shown to have significantly lower numbers of fecal bifidobacteria compared to healthy infants [58]. Allergy prevention via supplementation with lactobacilli and bifidobacteria therefore appeared promising. Probiotics and prebiotics have since become of the main strategies in allergy prevention in young infants.

**Probiotics**

The increase in allergic disorders has commonly been explained by a lack of early microbial stimulation of the immature immune system. The effects are mediated via the innate immune system (Toll-like receptors), resulting in the promotion of T helper 1 differentiation, production of regulatory cytokines (IL-10 and TGF-β) and enhanced intestinal IgA responses [59]. Several studies have demonstrated that perinatal administration of probiotics to mothers in the last weeks of pregnancy and to infants in the first few months of life was associated with a significant reduction in atopic eczema [25, 26, 60]. Nevertheless, results have been varied, depending on the probiotic strain, dose, timing and food matrix used. A study using *Lactobacillus acidophilus* (LAVRI A1) showed a paradoxical increase in allergic sensitization [61]. These studies highlight that outcomes depend considerably on the specific probiotic strains used. The role of probiotics in allergy prevention requires further study [62].

**Prebiotics**

Complex nondigestible, prebiotic oligosaccharides contained in breast milk provide the unique substrate for bifidobacteria. Infant formulas are usually devoid of such prebiotic oligosaccharides [63]. In recent years, manufactured long-chain fructo-oligosaccharides (FOS) and short-chain galacto-oligosaccharides (GOS) have been added to infant formulas and weaning solids. GOS and FOS promote fecal bifidobacteria in formula-fed infants [64, 65]. A randomized study examined the effects of a FOS/GOS-supplemented hydrolyzed formula on atopic eczema in 259 formula-fed infants during the first 6 months of life [66]. In the study, the FOS/GOS group had significantly lower rates of eczema than the placebo group, but eczema severity was similar for both treatment arms. A more recent European multicenter randomized controlled trial assessed the effect of prebiotics in healthy, low-risk infants from 8 weeks to 12 months [67].
Infants were randomized to standard infant formula supplemented with GOS, FOS and pectin-derived acidic oligosaccharides (n = 414) versus unsupplemented standard formula (n = 416). Prebiotics reduced the incidence of atopic dermatitis by 44% at 12 months, although disease severity was not affected. The number needed to treat in order to prevent one case of atopic dermatitis was 25 infants. Further studies are needed to assess the role of prebiotics in allergy prevention [68].

**Immune-Modulating Micronutrients**

Several immune-modulating micronutrients are of potential relevance in the prevention of food allergy, including omega-3 long-chain polyunsaturated fatty acids (LC-PUFA; fish oil) and vitamin D.

**Omega-3 Long-Chain Polyunsaturated Fatty Acids**

Maternal diets high in omega-3 LC-PUFAs are thought to have a protective effect against the development of allergies in the newborn [69]. Supplementation with docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) during pregnancy has been shown to increase LC-PUFA concentrations in breast milk [70]. A large randomized clinical trial of maternal fish oil supplementation during pregnancy demonstrated a significant decrease in cord blood concentrations of Th-2 cytokines (IL-4 and IL-13) as well as increased levels of oral tolerance-inducing TGF-β [71]. Palmer et al. [72] assessed the effect of high-dose fish oil supplementation in high-risk infants (i.e. family history of atopy). Infants were randomized to receive either 800 mg DHA plus 100 mg EPA (n = 368), or vegetable oil (n = 338). Supplements were administered to pregnant mothers from 21 weeks’ gestation until delivery. Infants were followed to 12 months of age and assessed for allergies by blood and skin testing. Primary outcomes were eczema and food sensitization. Infants in the fish oil-supplemented group had significantly lower rates of atopic eczema (7 vs. 12%; p = 0.04) and egg sensitization (9 vs. 15%; p = 0.02). This study highlights that fish oil supplementation during the second half of the pregnancy may provide an effective strategy to reduce the risk of eczema and food sensitization.

In another study by the same group [73], 420 high-risk infants were randomized to DHA 280 mg plus EPA 110 mg daily, or olive oil (control) from birth to 6 months of age. Between-group comparisons revealed no differences in allergic sensitization, eczema, asthma or food allergy. While postnatal fish oil supplementation improved infant ω-3 fatty acid status, it did not prevent childhood allergic disease. This finding is in keeping with an earlier Swedish study that
failed to find a preventive effect of postnatal omega-3 or omega-6 fatty acid exposure on eczema, asthma or atopic disease [74]. In summary, fish oil supplementation during pregnancy reduced the risk of atopic eczema and food sensitization, whereas dietary fish oil supplementation of the infant after birth was ineffective.

**Vitamin D**

Vitamin D is thought to be an important modulator of allergy risk in young infants [75, 76]. A recent Australian study showed that vitamin D insufficiency (serum level <50 nmol/l) was associated with a significantly increased risk of egg and/or peanut allergy [77]. This finding concurred with the observation that the prevalence of food allergy and eczema follows a North-South gradient, being more common in regions with less sun exposure and lower skin-derived vitamin D levels [78]. Adequate vitamin D levels in the first year of life may therefore provide protection against the development of food allergies. By contrast, vitamin D may also have undesirable immune-modulating effects and, in high doses, increase the risk of allergic sensitization. Vitamin D has been shown to inhibit the maturation of dendritic cells and impede the development of T helper 1 responses. In theory, vitamin D therefore could increase the risk of allergic disorders in infancy [79]. This is supported by a recent German birth cohort study (LINA study) which found that high vitamin D levels during pregnancy and at birth were associated with an increased risk of food allergy [80]. The varying effects of vitamin D on allergy risk have been explained by a U-shaped dose-response curve, whereby normal vitamin D levels may confer a protective effect and higher levels may increase the allergy risk [76]. The aforementioned studies suggest that both vitamin D insufficiency and oversupplementation are risk factors for allergies [75]. A well-designed, prospective randomized trial is needed to assess the role and optimum dosage of vitamin D supplementation in pregnant women and young infants.

**Conclusions**

Tolerance development and allergy risk are influenced by a complex array of factors, including genetics, epigenetic imprinting, microbial environment and other environmental factors. Strategies to promote early gut colonization with diverse, bifidobacteria-rich fecal microbiota include breastfeeding, avoidance of surgical deliveries or of perinatal antibiotics (where possible), and living in a rural farm environment. Exclusive breastfeeding for 6 months, use of hydrolyzed formula when breastfeeding is not possible, and the delayed introduction of
complementary feeding from 4 to 6 months remain the main strategies in primary prevention of dietary allergy. Several studies have demonstrated a beneficial effect of probiotics, particularly in the prevention of atopic dermatitis. The role of prebiotics in food allergy prevention is at this stage less clear. LC-PUFA supplementation (fish oil, DHA, EPA) during pregnancy has been shown to stimulate regulatory T cell responses and may reduce the risk of atopic dermatitis and egg sensitization. Fish oil supplementation in the newborn had no preventive effect for later allergic disease. The role of vitamin D supplementation during pregnancy and early infancy for the purpose of allergy prevention requires further study.

Disclosure Statement

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References


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