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Dietary exposures and allergy prevention in high-risk infants

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Abstract

Infants at high risk for developing a food allergy have either an atopic condition (such as eczema) themselves or an immediate family member with such a condition. Breastfeeding should be promoted and supported regardless of issues pertaining to food allergy prevention, but for infants whose mothers cannot or choose not to breastfeed, using a specific formula (i.e., hydrolyzed formula) is not recommended to prevent food allergies. When cow's milk protein formula has been introduced in an infant's diet, make sure that regular ingestion (as little as 10 mL daily) is maintained to prevent loss of tolerance. For high-risk infants, there is compelling evidence that introducing allergenic foods early—at around 6 months, but not before 4 months of age—can prevent common food allergies, and allergies to peanut and egg in particular. Once an allergenic food has been introduced, regular ingestion (e.g., a few times a week) is important to maintain tolerance. Common allergenic foods can be introduced without pausing for days between new foods, and the risk for a severe reaction at first exposure in infancy is extremely low. Pre-emptive in-office screening before introducing allergenic foods is not recommended. No recommendations can be made at this time about the role of maternal dietary modification during pregnancy or lactation, or about supplementing with vitamin D, omega 3, or pre- or probiotics as means to prevent food allergy.

Keywords: Breastfeeding, Food allergy, Infants

Introduction

The self-reported prevalence of food allergy in Canada is approximately 6% [1], and food allergy has increased over the past few decades [2]. Recent evidence suggests that preventing the development of food allergies in infants is possible. Several studies [3, 4], and one meta-analysis [5], have supported the early introduction of allergenic foods (in particular peanut and cooked egg) as a means of preventing allergies to those foods. This revised statement replaces a previous Canadian Paediatric Society (CPS) document from 2013 [6] and expands on a 2019 CPS practice point on this topic [7]. Recent research supports stronger recommendations than previously, for the active introduction of allergenic foods early in life. Further, there is now compelling evidence that warrants changing other, related recommendations, including the definition of an infant at high risk for developing allergic conditions [3, 8], the role of pre-emptive screening [8–12], the role of hydrolyzed formula [13, 14]] for allergy prevention, and the preventive role of breastfeeding in balance with the early introduction of solid foods [15–17].

Defining risk

There is no international consensus on the definition of infants at high risk for food allergy development. The CPS practice point defines an infant at high risk as having either a personal history of atopy or a first-degree relative

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(at least one parent or sibling) with an atopic condition (such as asthma, allergic rhinitis, food allergy, or eczema) [7]. That definition is used here, too, because it is broader than those based solely on family history [6, 18], and reflects the increasing evidence that the infants most at risk for developing food allergy have a personal history of eczema or other food allergy [19–22]. This inclusive definition also reflects the definition used by the National Institutes for Allergy and Infectious Diseases (NIAID) for an infant at high-risk of peanut allergy as having severe eczema and/or egg allergy [8]. It is important to remember, however, that food allergy can occur in infants with no specific risk factors [23].

Breastfeeding, and maternal diet during pregnancy and lactation

The available research trials examining the role of maternal allergen ingestion during pregnancy and lactation are observational studies that have demonstrated inconsistent results (Table 1). Systematic reviews of these observational trials have shown no link between maternal dietary intake and food allergy outcomes in children [24, 25]. Some study authors have noted limitations of methods, analysis, and inclusion criteria that have hampered results [26], with one recent systematic review concluding there was "no good evidence to recommend that pregnant or breastfeeding women should change their diet to prevent allergies in infants at high or normal risk" [26, 27]. Specific to peanut allergy, recent studies suggest that mothers ingesting peanut during breastfeeding may decrease the risk of peanut sensitization, provided this is coupled with the early introduction of peanut in the infant's diet [28, 29]. However, these studies are insufficient to support a recommendation to actively ingest peanut protein during breastfeeding. That there is no benefit to maternal dietary avoidance during pregnancy or lactation has been established, with one Cochrane review not only noting no reduction in atopic disease but possible harms, including a trend toward increased risk for preterm labour or low birth weight [25]. Randomized controlled trials (RCTs) are ongoing that will better inform this issue [30, 31]. Evidence that modifying the maternal diet during pregnancy and breastfeeding is an effective strategy to prevent food allergy is therefore lacking.

The data on breastfeeding itself as a food allergy prevention strategy are also mixed. Some studies have supported breastfeeding as a means to prevent allergy, while others have found no association [32–34]. Limitations in the breastfeeding literature include studies that were solely observational, inconsistent breastfeeding durations, and variable diagnostic criteria for food allergy.

For many health promoting reasons other than to prevent food allergy [18], the World Health Organization (WHO) and other leading international bodies [6, 35], support exclusive breastfeeding for an infant's first 6 months, and continued complementary breastfeeding up to age 2 years and beyond [36, 37].

Choice of formula

There is insufficient evidence at this time to advise on the use of specific formulas, such as hydrolyzed formulas, for allergy prevention. To prevent atopic conditions generally, previous guidelines have recommended the use of hydrolyzed formulas when mothers could not, or chose not to, breastfeed [6, 18]. However, a recent Cochrane review found no evidence to support short-term or prolonged hydrolyzed formula feeding (compared with exclusive breastfeeding) to prevent atopic disease [38]. Also, one recent meta-analysis found no evidence that any hydrolyzed formula, whether partially or extensively

Table 1 Exposures and associations with food allergy prevention

Exposure	Does contribute	Does not contribute	Highest level of study evidence	Quality of evidence
Maternal peanut ingestion during pregnancy and breastfeeding	−	+	Observational	B
Probiotics	−	+	RCT	C
Breastfeeding	−	++	Observational	B
Hydrolyzed formula	−	+++	Observational	B
Early allergenic food introduction for infants (peanut at 4–11 months of age; egg at 4–6 months)	+++	−	RCT	A
Vitamin D supplementation	−	+	Observational	B

GRADE Working Group. Quality of Evidence: A (Further research is unlikely to change this recommendation); B (Further research is likely to have an impact on our confidence in this recommendation); C (Further research is very likely to have an important impact on our confidence in this estimate of effect)

Based on scoping review of the literature to date on a scale of: − < + < ++ <+++

RCT Randomized controlled trial

Source: [75] Adapted with permission

hydrolyzed, prevented any atopic conditions, including food allergy [13]. Current evidence does not favour using hydrolyzed formulas rather than intact cow's milk formula to prevent atopic conditions.

Regarding cow's milk formula specifically, three observational studies have documented increased risk for developing cow's milk allergy with delayed or irregular ingestion of cow's milk early in life [39–41]. One recent RCT of 504 infants in Japan found that ingesting a minimum of 10 mL of cow's milk formula at least once every day (compared with avoiding cow's milk formula supplementation) at 1–2 months of age significantly reduced cow's milk allergy at 6 months of age (0.8% versus 6.8%, risk ratio (RR) 0.12, 95% confidence interval (CI) 0.01–0.50; probability (P) < 0.001). Moreover, cow's milk formula did not 'compete' with breastfeeding. Approximately 70% of infants from both groups were still breastfeeding at 6 months of age [42]. Both groups had frequent cow's milk formula exposure in the first month of life, and the evidence suggested that stopping cow's milk formula feeds in the second month increased the risk for developing cow's milk allergy. Therefore, practitioners and families should be aware that irregularly supplementing breastfeeding with cow's milk formula may increase risk for cow's milk allergy. If cow's milk formula is introduced, regular ingestion (as little as 10 mL daily) should be maintained to prevent loss of tolerance [42].

Introducing solid foods

Several observational studies have found an association between early ingestion (at less than 6 months of age) of a specific food allergen (in particular cow's milk, egg, and peanut) and lower rates of allergy to that food in childhood [43–45]. Studies conducted since 2013, including RCTs, have provided convincing evidence for the early introduction of allergenic foods to prevent food allergy in high-risk infants.

A significant 'leap' forward in this field was the Learning Early About Peanut (LEAP) study in infants at high risk for peanut allergy [3], which randomized 640 infants with severe eczema or egg allergy (or both) to either early peanut ingestion (at 4–11 months) or avoidance until 5 years of age. Results demonstrated an 80% reduction in peanut allergy with early peanut ingestion [3]. The LEAP study found a preventative effect in both skin test-negative (13.7% versus 1.9%; P < 0.001) and skin test-positive infants (35.3% versus 10.6%; P = 0.004), which supported early peanut introduction as a means of both primary and secondary prevention. One recent meta-analysis and systematic review confirmed with moderate certainty that introducing peanut early (at 4–11 months) is associated with reducing peanut allergy (RR0.29; 95% CI: 0.11–0.74) [5].

Five RCTs have examined early egg introduction in high-risk infants to prevent egg allergy, with discrepant results, perhaps because egg was ingested in different forms. The only RCT to examine early cooked egg ingestion (the PETIT study) randomized 147 infants with eczema to either egg ingestion at 6 months of age or avoidance until one year of age, and found a significant reduction in egg allergy with earlier ingestion (RR 0.222; 95% CI: 0.081–0.607; P = 0.0012) [4]. By contrast, four RCTs examining early pasteurized raw egg ingestion failed to show a preventative effect against egg allergy, or revealed a high rate of adverse events, or both [46–49]. One meta-analysis and systematic review reported with moderate certainty that early egg introduction (at 4–6 months) was associated with reduced egg allergy (RR 0.56; 95% CI: 0.36–0.87) [5].

Only one randomized trial, the Enquiring About Tolerance ('EAT') study, examined the early introduction of multiple allergenic foods (peanut, cow's milk, sesame, fish, wheat, egg) [23] in 1303 standard-risk infants. They were randomized to either early (at 3 months) or more typical (at 6 months) ingestion of all six allergens. No significant difference in the rate of food allergy was found between the two groups during the intention to treat analysis (5.6% versus 7.1% respectively; P = 0.32). Adherence was a significant issue in this study, however, at 42.8% overall.

Following the LEAP study, the NIAID released addendum guidelines which recommended that infants with severe eczema, egg allergy, or both have peanut introduced into their diet at 4–6 months of age [8]. For infants with mild to moderate eczema, the recommendation was for at-home introduction at around 6 months of age, and for infants without atopic risk factors, the recommendation was for introduction in accordance with parental preference and cultural norms. The CPS practice point also recommended that infants with either a personal or immediate family history of atopy be introduced to allergenic foods at about 6 (but not before 4) months of age [7, 10], in keeping with other international organizations, such as the Australasian Society of Clinical Immunology and Allergy [10].

There are still several areas of uncertainty. Introducing allergenic solid foods before 6 months of age to prevent food allergy in high-risk infants remains somewhat controversial in some contexts. The optimal amount of allergenic solid per serving is unclear, and evidence concerning other common allergenic foods (e.g., tree nuts, sesame, grains, soy, fish and shellfish) is lacking, although the mechanism of sensitization is believed to be similar. In infants with non-IgE-mediated food allergies

(i.e., food protein-induced enterocolitis syndrome [FPIES]), guidelines have recommended delaying introduction of allergenic foods such as egg and peanut to reduce the risk of FPIES in response to those foods [50]. However, because IgE-mediated food allergies are not only more prevalent but generally more difficult to outgrow, the risk for developing an IgE-mediated allergy to peanut or egg from delayed introduction is more concerning than the theoretical benefit of delayed introduction to manage FPIES [51]. Furthermore, the optimal frequency of allergenic solid ingestion remains unknown, although all the RCTs completed to date have required regular ingestion (typically several times a week) as a part of their protocols [3, 39, 40]. As noted above, the cow's milk formula studies have suggested that irregular exposure could increase the risk for developing cow's milk allergy [39–41]. While the frequency of ingestion of allergenic solids may be unclear, regularity appears to be important, with a few ingestions per week to promote ongoing tolerance being recommended by the CPS in 2019 [7].

There is no hard evidence of benefit for spacing out the introduction of different foods (by a certain number of days, for example), and some allergists may recommend introducing mixtures (e.g., different mixed tree nut butters) on a case-by-case basis, for convenience. A recent survey of paediatricians in the United States found that most did not counsel families to wait 3 days (or longer) between introducing foods, noting that the practice may limit infant food diversity and delay early peanut introduction [52].

Another potential drawback of introducing solid foods before 6 months is the potential impact on the total duration of breastfeeding and the benefits of exclusive breastfeeding. However, neither the LEAP nor EAT studies found that breastfeeding duration differed significantly among their test groups [3, 23], and one recent Canadian survey found that paediatricians and family physicians were largely unconcerned that earlier introduction of solid foods in infant diets would impact breastfeeding negatively [53].

Pre-emptive screening

The NIAID has recommended administering a pre-emptive skin prick test or specific IgE blood tests before introducing peanut to high-risk infants. The American Academy of Pediatrics (AAP) supported this recommendation in their own 2019 statement, but added that testing should "not be a deterrent or generate 'screening creep'" (e.g., by including lower risk infants with mild to moderate eczema as well as infants in the high-risk category) [8, 14]. However, these screening recommendations have not been adopted in leading British or Australasian guidelines, or in new North American consensus guidance [9, 10, 22]. Significant population-level testing limits, such as high rates of clinically irrelevant positive test results—and the lack of infant oral food challenges to exclude them [53]—make pre-emptive screening impractical [2, 54]. Long waiting lists [53, 55], low cost effectiveness [56, 57], the risk of 'screening creep' [58], and low parent stakeholder acceptance of this approach, are further impediments [53, 59, 60] to pre-emptive screening.

One Australian study on feasibility estimated that screening all infants considered to be at high risk for peanut allergy would require testing 16% of the infant population but would still miss 23% of peanut allergy cases [19]. Also, none of the LEAP infants in the early introduction arm experienced anaphylaxis at first ingestion, and no known fatalities following early introduction occurred [3]. Even if anaphylaxis were to occur at the first ingestion, one American study from 2018 showed that only 4% of infants experiencing anaphylaxis had truly severe symptoms, which was lower than in older children, and no fatalities were reported [61]. Another recent American study of food allergy-related emergency room visits found that infants presenting with anaphylaxis tended to do so after the first known ingestion of the offending food, and that children under 2 years of age were less likely to meet anaphylaxis criteria than older children [62]. Data from Australia published in 2019 has similarly shown high uptake of early peanut introduction with no pre-emptive-screening. A threefold increase in early peanut ingestion occurred in 2017/18 based on education alone, with 88.6% (95% CI: 86.1–90.7%) of infants having been introduced to peanut by 12 months of age compared with only 28.4% (95% CI: 27.2–29.7%) in 2007/11 [63]. The risk of having a severe reaction to peanut during at home introduction in infancy is extremely small (0.08%), and increasing awareness of this could assist with implementation of food allergy prevention [64, 65].

In Canada, there is insufficient evidence to support pre-emptive screening of allergenic foods prior to introducing into children's diets, and routine testing is not recommended. In-office or virtual [66] introduction of allergenic foods should only be considered for families who are very hesitant, despite education, to try this at home.

Other interventions

Several other interventions, including supplementation with vitamin D [67, 68], omega 3 [69, 70], and pre- or probiotics [71–74] are being studied as possible food allergy preventive measures, but the data are mixed and

no firm conclusions regarding these strategies can be made at this time.

Recommendations for clinicians

- Consider infants at high risk for food allergy when they have a personal history of atopy or a first-degree relative (at least one parent or sibling) with an atopic condition (such as asthma, allergic rhinitis, food allergy, or eczema).
- Promote and support breastfeeding for up to 2 years and beyond, regardless of issues pertaining to food allergy prevention.
- There is still insufficient evidence to recommend modifying the maternal diet to prevent food allergy (i.e., by avoiding or ingesting particular allergenic foods during pregnancy and while breastfeeding).
- For mothers who cannot or choose not to breastfeed, hydrolyzed formulas should not be recommended to prevent atopic conditions (e.g., eczema, asthma, allergic rhinitis) in either high- or low-risk infants.
- When cow's milk protein formula has been introduced in an infant's diet, make sure that regular ingestion (as little as 10 mL daily) is maintained to prevent loss of tolerance.
- For high-risk infants, encourage the introduction of allergenic foods (e.g., cooked [not raw] egg, peanut) early, at about 6 months and not before 4 months of age, in a safe and developmentally appropriate way, at home. In infants at low risk for food allergy, allergenic foods can also be introduced at around 6 months of age.
- New foods, including commonly allergenic foods, can be introduced on successive days, with no evidence of harm to this approach.
- When allergenic foods have been introduced, make sure that ongoing ingestion of age-appropriate serving sizes is regular (i.e., a few times a week), to maintain tolerance.
- Pre-emptive screening for infant food allergies is not recommended. Families should be counseled that the risk of a severe reaction on the first exposure to an allergen is extremely low.
- There is currently insufficient evidence to recommend vitamin D, omega 3, or pre- or probiotic supplements to prevent food allergies in infants.

Abbreviations

AAP: American Academy of Pediatrics; CPS: Canadian Pediatric Society; EAT: Enquiring About Tolerance; FPIES: Food Protein Induced Enterocolitis Syndrome; LEAP: Learning Early About Peanut; RCT: Randomized controlled trial.

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