Food allergy prevention through the decades: An ounce of humility is worth a pound of cure

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ABSTRACT

Food allergy prevention has undergone a significant transformation over the past 3 decades. This review provides an overview of the evolution of food allergy prevention, highlighting changes in guidance, cost-effectiveness of prevention, the role of shared decision-making, and the emergence of oral immunotherapy for those in whom primary prevention fails. Changes to food allergy prevention over recent decades can be conceptualized into five epochs, which have followed a general trend of loosening restrictions on the allergen introduction timeline. These epochs are characterized by significant maternal and infant dietary restrictions in the "universal avoidance epoch"(-1990), loosened maternal diet restrictions in the "infant avoidance epoch" (1990–2000), a time-bound allergen introduction schedule in the "stratified avoidance epoch" (2000–2010), retraction of recommendations in the "corrective retraction epoch" (2010–2015), and endorsement of early allergen introduction in the "early introduction epoch" (2015-present), the start of which is marked by the 2015 Learning Early About Peanut study. In hindsight, it is clear that certain recommendations from previous decades were not the best course of action. A no-screening early introduction approach to food allergy prevention is both cost-effective and beneficial to patient quality of life.

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Food allergy prevalence has increased significantly over the past 3 decades, with an estimated 18% increase in reported childhood food allergy incidence from 1997 to 2007.[1,2] Food allergy prevalence estimates in the 1990s of 3.4% have been surpassed by current estimates of 5-10%.[3–5] Although the prevalence varies by location, family history, and environment, it is generally accompanied by a risk of significant financial and psychosocial burden.[6–12] Food allergy prevention and treatment are therefore areas of high-impact active research, with the past several decades producing an evolving understanding of the pathophysiology and natural course of food allergy.[13–16] This paper aims to provide an overview of food allergy prevention guidelines over recent decades while also describing advances in treatment, cost-effectiveness, and the role of shared decision-making (SDM).

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Epochs of Prevention

Food allergy prevention guidance has changed significantly over time, with some current recommendations nearly opposite of those from 30 years ago. In large part, contemporary understanding of food allergy prevention has evolved in response to greater certainty of scientific evidence about prevention strategies. This paper conceptualizes these changes into five "epochs," with a focus on U.S. guidance (Figure 1).

Universal Avoidance Epoch: -1990

Before the 1990s, uncertainty existed with regard to the role of dietary avoidance during pregnancy and lactation in reducing the risk of infant food allergy. This uncertainty created a tendency toward universal avoidance of foods thought to be more allergenic in both mothers and infants. In 1989, a randomized controlled trial of 288 infants found that delayed allergenic food exposure for as long as 2 years combined with maternal avoidance of allergens during pregnancy and lactation significantly reduced infant food sensitizations in the

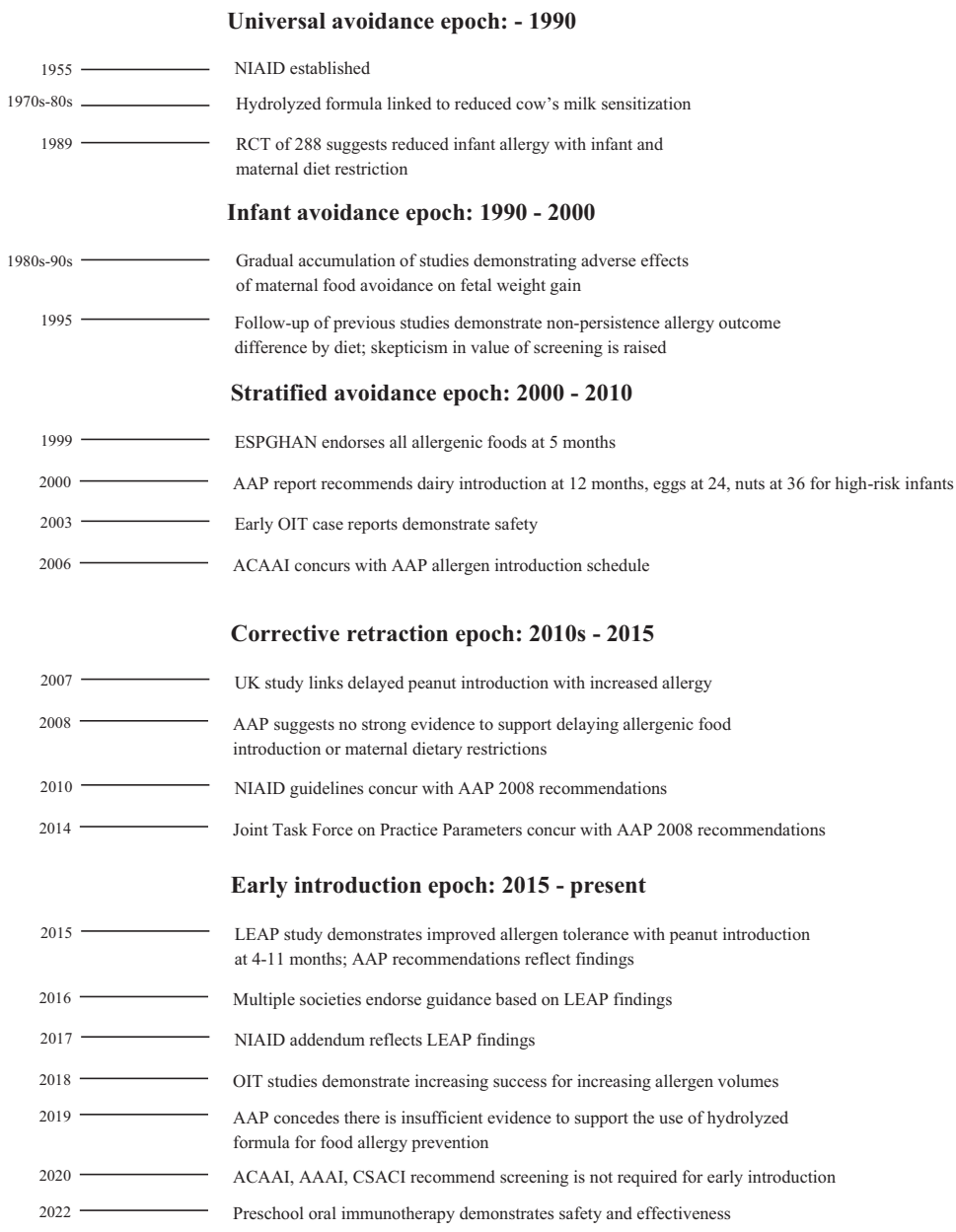

Figure 1. *Timeline of food allergy prevention.*

first year of life.[17] Although this study was notably limited by early atopy assessment at 12–24 months of age, it laid the foundation for a "universal avoidance epoch," characterized by prolonged allergen avoidance for both infants and mothers. The proposed logic for this was that infant predisposition to food sensitivity decreases with age. This perspective was bolstered by multiple exploratory studies conducted in the 1970s and 1980s, which proposed links between casein hydrolysate formula and reduced cow's milk sensitization.[18,19] Some research during this time provided evidence to the contrary, including a 1980 study of 375 children that found no link between early fish and/or citrus exposure and food allergy at 3 years.[20] However, these results and others like it were overshadowed by an approach of early and prolonged allergen avoidance.

Infant Avoidance Epoch: 1990–2000

The "universal avoidance epoch" gave way to the "infant avoidance epoch" in the 1990s, which was characterized by relaxation of maternal food restrictions. This epoch began with research that demonstrated the potential for adverse effects of maternal food avoidance on maternal and fetal weight gain but little effect on food allergy risk.[21–24] Changing perspectives on the maternal diet applied not only to pregnancy but to lactation as well with a prospective randomized study of 212 mothers, suggesting no difference in the incidence of food sensitization

between mothers with and those without lactation diet restriction.[21,22] Follow up of previous studies, including that conducted by Zeiger *et al.*[25] in 1989, further supported this perspective with the finding that, at 7 years of age, no differences in food allergy rates existed between patients who were allergen exposed and patients who were allergen restricted (n = 165). This finding cast further doubt on the notion that specific immunoglobulin E levels could reliably predict food allergy, prompting initial skepticism toward the value of screening. In 2000, a Cochrane review became the first article to conclude that "Prescription of an antigen avoidance diet to a high-risk woman during pregnancy is unlikely to reduce substantially her risk of giving birth to an atopic child. Moreover, such a diet may have an adverse effect on maternal and/or fetal nutrition."[24] Nevertheless, an approach that favors infant food avoidance would continue under the continued logic that delayed allergen exposure would hasten tolerance.[26,27] Notably, a 1998 American Academy of Pediatrics (AAP) report[28] was unusually prescient for the time, which concludes that soy formula in the infant diet had no proven value in prevention of atopic disease in healthy infants at high risk.

Stratified Avoidance Epoch: 2000–2010

The 1998 AAP report on the use of soy formula notwithstanding, the early 2000s marked a shift into the "stratified avoidance epoch," which was characterized by continued allergen avoidance recommendations for infants, now stratified across time and perceived allergy risk. It was recommended that dairy be introduced at 12 months; eggs at 24 months; and other allergens, such as nuts and seafood, at 36 months in infants at high risk for development of food allergy.[27] This perspective, based on expert consensus and initially forwarded in a 1998 document by the United Kingdom Food Standards Agency, was similarly adopted by the AAP in 2001, and also later endorsed by American College of Allergy, Asthma and Immunology (ACAAI) in 2006.[27,29,30] The European Society for Pediatric Allergology and Clinical Immunology and European Society for Pediatric Gastroenterology, Hepatology, and Nutrition adopted a more progressive recommendation that solid foods simply be started at 5 months of age.[31] Notably, the Joint Task Force on Practice Parameters also took a more measured approach to the recommendations and cautioned that "the effectiveness of these strategies for safeguarding against the development of food allergies has not been established."[32] As was true of the preceding epochs, there remained a paucity of blinded, controlled, multicenter trials, and, as such, recommendations were noted to be considered provisional and directed only at infants at high risk.

Corrective Retraction Epoch: 2010s-2015

A "corrective retraction epoch" emerged in the late 2000s and early 2010s, characterized by the retraction of previous recommendations without definitive replacement based on observational studies that suggested that early introduction was protective but that could not infer causality. As such, this epoch was marked by a move toward equipoise. The makings of this epoch began in 2007 with a U.K. study that noted an increase in peanut allergy incidence during the period when delayed peanut introduction was recommended.[33] Further evidence from the KOALA Birth Cohort Study,[34] which involved 2558 infants and demonstrated that greater delay in cow milk introduction was associated with a higher rate of eczema and atopic disease, questions the paradigms of avoidance. In addition, the prospective LISA Birth Cohort[35] found no evidence to support delayed solid introduction beyond 4 to 6 months, finding that food sensitization rates were greater in children with a more delayed introduction. In 2008, Du Toit *et al.*[36] used two separate questionnaires to assess peanut allergy prevalence in Jewish schoolchildren (5171 in the United Kingdom and 5615 in Israel) and infant peanut consumption (77 in the United Kingdom and 99 in Israel). The investigators demonstrated a 10-fold difference between self-reported peanut allergy prevalence in Israeli and U.K. school children (1.85% versus 0.17%; $p < 0.001$), despite earlier peanut introduction with more frequent consumption of peanut-containing Bamba snacks in Israel.[36] The median retrospectively reported peanut consumption in infants ages 8 to 14 months of age was close to 7.1 g Israel eight times per month in Israel versus no consumption in the United Kingdom ($p < 0.001$).[36] With such evidence against a protective avoidance effect accumulating, the AAP revised its infant feeding recommendations in 2008, stating that strong evidence in support of delaying allergenic food introduction or maternal dietary restriction was limited, although this document stopped short of actively advocating for early introduction.[37] Further evidence against delayed introduction emerged in a 2010 cross-sectional Australian study, which noted a 3.4-fold increase in egg allergy when egg was introduced at 12 months versus 4–6 months.[38] The 2010 National Institute of Allergy and Infectious Diseases (NIAID) recommendations also cautioned against delayed introduction of common allergens beyond 4–6 months of age but also hedged to recommend early introduction.[39] However, in 2013, the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma, and Immunology (AAAAI) advised that complementary foods may be introduced between 4 and 6 months of age, and the Joint Task Force on Practice Parameters 2014 food allergy practice parameter stated

"Do not recommend maternal allergen avoidance or avoidance of specific complementary foods at weaning because these approaches have not proved effective for primary prevention of atopic disease."[39–41] Thus, this epoch de-emphasized and recommended against former recommendations for delayed allergen exposure, but it did not explicitly endorse early allergen introduction.

The Early Introduction Epoch: 2015–2022

The "early introduction epoch" has been characterized by emergence of higher-certainty evidence in favor of allergen introduction as early as 4 months. This epoch was launched by the results of the LEAP study, the first published randomized controlled trial to show a significant (>80%) relative risk reduction of peanut allergy with peanut introduction between 4 and 11 months compared with late introduction at 5 years.[42] The LEAP study led to consensus recommendations in favor of immediately recommending cautious peanut introduction between 4 and 11 months of age for infants at high risk but pending more formal evidence-synthesis to craft an updated infant feeding policy.[43] These new placeholder recommendations represented a large consensus among the AAP, AAAAI, ACAAI, Australasian Society of Clinical Immunology and Allergy (ASCIA), Canadian Society of Allergy and Clinical Immunology (CSACI), European Academy of Allergy and Clinical Immunology, Israel Association of Allergy and Clinical Immunology, Japanese Society for Allergology, Society for Pediatric Dermatology, and the World Allergy Organization.[43] This interim consensus recognized the importance of the LEAP study findings but stopped short of recommending how to implement these findings, which each stakeholder organization felt was subject to more country-specific nuancing, with particular attention to be paid to areas were peanut allergy was not endemic and there was concern that established feeding practices could be unnecessarily disrupted in such areas.

An example of such country-specific guidance was developed by an NIAID expert panel in 2017. This panel recommended a risk-stratified approach to early introduction in which screening testing was encouraged in patients with egg allergy or severe eczema before early introduction and regular consumption of non-chokable peanut products. However, this modified screening approach from the LEAP study was never itself studied or proven necessary.[44] Although seemingly a large step forward at the time that attempted to provide some safety measure against initial reactions in infants, it later became clear that this guidance may have been a step backward in that it reversed delayed introduction guidance at the cost of introducing a poorly evidenced, inefficient, and infeasible screening algorithm.[41,45,46] When evaluated under a population-level simulation, analysis of the data showed that the screening approach might actually increase a diagnosis of peanut allergy. Moreover, analysis of survey data from parents and clinicians suggested that the screening algorithm was difficult to follow and would have poor adherence and acceptability.[47,48] A 2018 Markov model demonstrated that a no-screening approach with universal early peanut introduction had superior health and economic benefits than a screening or delayed introduction approach, with a decreased number of peanut allergy cases (>3200 fewer, due to not using a diagnostic cutoff and allowing all persons to objectively fail introduction), increased number of quality adjusted life years, and decreased health-care costs (>$650,000,000 savings over a 20-year horizon).[48] Analysis of the Australian HealthNuts database supported this perspective finding that, even if all infants with early onset eczema and/or egg allergy were screened for peanut allergy, 23% of peanut allergy cases would still be missed from lower-risk populations.[49] This study concurred that there are "major cost and logistic challenges" to screening all infants at risk for peanut allergy at a population level.[49] Subsequent studies have demonstrated real-world evidence that misapplication and misuse of screening strategies have led to increases in over-testing for non-peanut allergens (*e.g.*, "screening creep," which the NIAID guidelines specifically do caution against), contributing to food allergy overdiagnosis.[45,46,50–52]

With an evolved understanding of the risk and ramifications of overdiagnosis, contemporary guidance from the AAAAI, ACAAI, and CSACI advises the introduction of potentially allergenic foods as early as 4–6 months for the purpose of food allergy prevention and suggests that screening tests are not required before a first food introduction (Table 1).[53,54] This guidance is aligned with most other international guidance with regard to how to implement early introduction.

An "eat early and eat often approach" likely applies to a broad and diverse diet. For example, a U.K. randomized controlled trial of 1303 infants found the per-protocol rate of peanut allergy to be significantly lower in children at standard risk to peanuts as early as 3 months of age compared with those who were exclusively breast-fed until 6 months, with a greater effect suggested among those complying with higher-frequency, higher-quantity ingestion (from *post hoc* analysis).[55] Benefit of early introduction extends to other foods as well. For example, in 2017, the PETIT trial demonstrated benefit of small amounts of regular cooked egg introduction to infants.[56] More recent data from the PreventADALL study have also shown similar effects with respect to very early introduction (*e.g.*, between 3 and 6 months of life).[57]

Along with a push for early introduction, this epoch has also significantly de-emphasized recommendations for use of hydrolyzed formula for prevention, with 2019 AAP recommendations stating that there is

Table 1 **A consensus approach to the primary prevention of food allergy through nutrition: guidance from the American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma and Immunology; and the Canadian Society for Allergy and Clinical Immunology***

Question	Recommendation	Strength
1. What criteria define an infant at high risk for the development of food allergy?	Recommendation 1. Consider infants with severe eczema at the highest risk of developing a food allergy. Consider infants with mild-to-moderate eczema, a family history of atopy in either or both parents, or infants with one known food allergy potentially at some increased risk of developing food allergy (or an additional food allergy). Be aware that food allergy often develops in infants who have no identifiable risk factors. There is no evidence to clearly support that the younger sibling of a child with peanut allergy is at increased risk of developing peanut allergy, although such infants may be at risk of developing peanut allergy secondary to delayed introduction of peanut.	Recommendation 1: moderate; strength of Recommendation 1: B; evidence category: IIa-IV; risk of bias: moderate
2. What is the evidence that supports the timing of the introduction of potentially allergenic complementary foods and the development of IgE-mediated food allergy?	Recommendation 2. Introduce peanut-containing products to all infants, irrespective of their relative risk of developing peanut allergy, starting at ~6 months of life, although not before 4 months of life. Introduction can occur at home when the infant is developmentally ready for complementary food introduction, in accordance with the family's cultural practice, but not before the infant demonstrates developmental readiness with eating a few other common starter foods. Although screening peanut skin or sIgE testing and/or in-office introduction is not required for early introduction, this remains an option to consider for families who prefer to not introduce peanut at home; this decision is preference sensitive and should be made when taking into account current evidence and family preferences. Strongly consider encouraging either home introduction or offering a supervised oral food challenge for any positive SPT or sIgE result. Once peanut is introduced, regular ingestion should be maintained.	Recommendation 2: strong; strength of Recommendation 2: A; evidence category: Ia-III; risk of bias: moderate
	Recommendation 3. Introduce egg or egg-containing products to all infants, irrespective of their relative risk of developing allergy, ~6 months of life, although not before 4 months of life. Use only cooked forms of egg and avoid administering any raw, pasteurized egg-containing products. Introduction can occur at home when the infant is developmentally ready for complementary food introduction, in accordance with the family's cultural practice but not before the infant demonstrates developmental readiness with eating a few other common starter foods. Although screening egg skin or sIgE testing and/or in-office introduction is not required before early cooked egg introduction, this remains an option to consider for families that prefer to not introduce egg at home; this decision is preference-sensitive and should be made by taking into account current evidence and family preferences. Strongly consider encouraging home introduction, or offering a supervised oral food challenge for any positive SPT or sIgE result. Once egg is introduced, regular ingestion should be maintained.	Recommendation 3: strong; strength of Recommendation 3: A; evidence category: Ia-III; risk of bias: low

Table 1 **Continued**

Question	Recommendation	Strength
	Recommendation 4. Do not deliberately delay the introduction of other potentially allergenic complementary foods (CM, soy, wheat, tree nuts, sesame, fish, shellfish), once introduction of complementary foods has commenced at ~6 months of life but not before 4 months. There may be potential harm in delaying the introduction of these foods based on past observational studies. There are no data that show harm in introducing these other allergenic foods within the first year of life but also no data to suggest specific benefit. Before early introduction of these foods, screening skin or sIgE testing and/or in-office introduction is not required; however, the decision to screen or not is preference sensitive and should be made by the clinician taking into account current evidence and family preferences. Strongly consider encouraging home introduction or offering a supervised oral food challenge for any positive SPT or sIgE result if screening is performed. Once introduced, regular ingestion should be maintained.	Recommendation 4: moderate; strength of Recommendation 4: A/B; category of rvidence: Ib-IV; risk of bias: moderate
3. Is there an association between early infant diet diversity and the development of food allergy?	Recommendation 5. On introducing complementary foods, infants should be fed a diverse diet because this may help foster prevention of food allergy. There is observational evidence but not any RCTs that support this recommendation, but this is balanced by no known harm in introducing a diverse range of foods. Future evidence may more conclusively demonstrate specific potential health benefits of diet diversity. In accordance with Recommendation 4, do not deliberately delay the introduction of other potentially allergenic complementary foods (CM, soy, wheat, tree nuts, sesame, fish, shellfish) once introduction of complementary foods has commenced at ~6 months of life, but not before 4 months.	Recommendation 5: weak; strength of Recommendation 5: C; evidence category: IIb-III risk of bias: high
4. What is the role for the use of hydrolyzed formula for the prevention of food allergy?	Recommendation 6. Do not routinely prescribe or recommend the use of any HFs for the specific prevention of food allergy or development of food sensitization.	Recommendation 6: strong; strength of Recommendation 6: A; evidence category: Ia-IV; risk of bias: moderate
5. What are the roles of prenatal food exposures, postnatal food exposures while breast-feeding an infant, and breast-feeding in general on the development of food allergy?	Recommendation 7. We do not recommend maternal exclusion of common allergens during pregnancy and lactation as a means to prevent food allergy. We offer no recommendation to support any particular food or supplement in the maternal diet for the prevention of food allergy in the infant in either the prenatal period or while breast-feeding. Although exclusive breast-feeding is universally recommended for all mothers, there is no specific association between exclusive breast-feeding and the primary prevention of any specific food allergy.	Recommendation 7: weak; strength of Recommendation 7: B/C; evidence category: Ia-IV; risk of bias: high

IgE = Immunoglobulin E; sIgE = specific IgE; SPT = skin-prick test; CM = cow's milk; RCT = randomized controlled trial; HF = hydrolyzed formula.
**Reproduced with permission from Ref. 53.*

insufficient evidence to support the use of hydrolyzed formula in the first year of life for food allergy prevention in infants at high risk and the joint Canadian/U.S. guidance recommending against routine use of hydrolyzed formulas for allergy prevention.[53,58]

Looking Forward: Optimization of Early Introduction, 2023, and Beyond

Overall, the epochs of food allergy prevention have trended toward loosening restrictions on the timing of allergen introduction as evidence to support this has evolved. Analysis of preliminary research suggests that there is room for further optimization of successful early infant introduction and that the quantity and frequency of introduction may be important. Recent CSACI guidelines[59] emphasize the importance of not just early introduction but also of continued consumption of potentially allergenic foods. This may be a critical aspect to early introduction, as evidenced by the Australian EarlyNuts experience, which noted that, although there was an increase in early peanut introduction in the year after the Australasian Society of Clinical Immunology and Allergy 2016 guidelines, only 28% of infants were consuming peanut more than one time per week.[60] The low frequency of regular consumption may explain the finding that population prevalence of peanut allergy has not decreased as much as expected.[61] Less-frequent allergen consumption raises the question of whether a greater preventative effect could be achieved with more frequent exposure, although such effects remain unknown, and have only been demonstrated in *post hoc* analysis from adherent populations in the EAT, LEAP, and LEAP peanut allergy screening study.[42,55] If there indeed is a necessary quantity and frequency for prevention, then this may raise questions if early introduction actually represents prevention or desensitization. Regardless, it is important that clinicians encourage families not merely to introduce potential allergens early but also to continue regular consumption of tolerated foods. In addition, although many recommendations on maternal food avoidance have been clarified, research to date has not rigorously supported recommendations for maternal food inclusion, *i.e.*, the potential benefit of prenatal supplements such as vitamin D, omega-3 fatty acids, dietary fiber, prebiotics, and probiotics.[62–64] The role of the gut microbiome is similarly underexplored, although early evidence implicates a potential role of gut dysbiosis in allergy development.[65,66] Similarly, a role for diversity in the early infant diet may also be contributory.[67,68] Overall, the future of food allergy prevention is trending toward continued relaxation of infant avoidance, with more focus on other modification factors that may enhance these effects in specific populations.

When Primary Prevention Fails – Rescue Refeeding Through Infant Oral Immunotherapy

Not all children will benefit from early introduction. This strategy is meant to prevent the risk of allergy development but will not prevent all cases. For these infants, there needs to be a focus on how to treat food allergy beyond strict avoidance. Available therapy options such as oral immunotherapy (OIT) are a potential path forward.[69–71] Although introduced as a concept in the early 20th century, OIT has gained momentum as a practical treatment option over the past 18 years.[71–73] There is evidence that suggests that OIT is safe and effective in infants and preschool children, which offers a potential option for early treatment.[74,75] Starting OIT early is one way to bridge the gap between early introduction and treatment. In a real-world study of preschool peanut OIT, therapy seemed safest in infants, with 81% of children tolerating 4 g of peanut protein and all the patients tolerating 1 g.[76] No infants had severe reactions.[76] Similarly, the 2022 IMPACT trial, a placebo controlled RCT, showed good safety and efficacy, similar to OIT trials in older children.[74,75] A paradigm of salvage OIT has been proposed for children who fail early introduction in an effort to improve health and economic outcomes for children with food allergies and reduce the time lived without active disease management (Figure 2).[69,70]

Cost-Effective Care

The impact of food allergy is far-reaching, with effects on individuals, families, communities, and the health-care system at large.[77] However, there is value gained from early introduction and potential treatment approaches that can help reduce this burden.[78,79]

Cost of Allergy Care

The cost of food allergy treatment was comprehensively examined in a 2013 cross-sectional survey, which estimated a total annual cost of $24.8 billion ($4184 per year per child) in the United States. Families were identified as bearing most of this cost (83%) due to both direct out-of-pocket and opportunity costs.[7] An updated analysis from 2022 suggested a cost of $7049 per individual for peanut allergy with costs that range between $6517 and $14,424 for the major nine allergens.[80] This significant economic burden is not unique to the United States; however, there is evidence that involvement of an allergy expert can alleviate both costs and burden of disease.[9,80–82]

Cost of Early Introduction Versus Screening

The significant cost of allergy care has prompted investigation into the cost-effectiveness of allergy prevention, namely screening versus no-screening

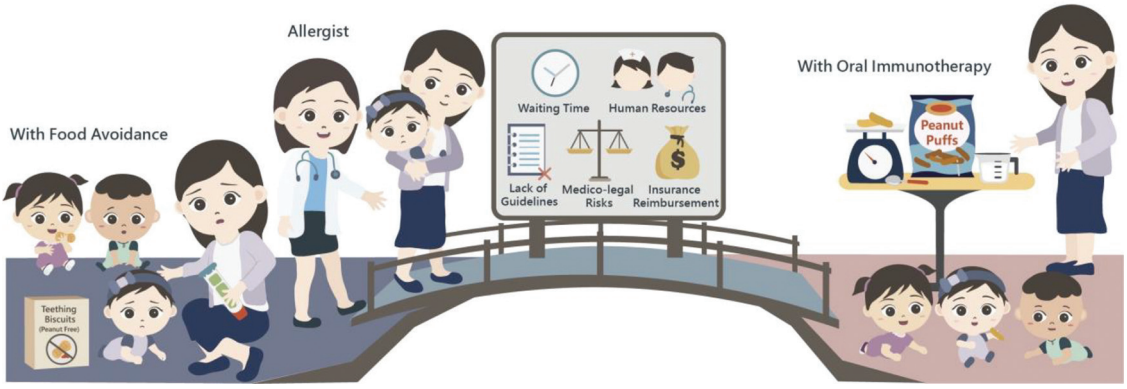

Figure 2. *Challenges and opportunities of early food immunotherapy. (Reproduced with permission from Ref. 69.)*

approaches (Table 2). The aforementioned 2018 Markov model on the value of early introduction screening found universal introduction without screening to yield savings of $1019 per individual when compared with skin test screening, with U.S. societal savings of $654 million over a 20-year period.[48] Delayed introduction was identified as the least cost-effective option.[48] Similar findings apply to egg allergy, with savings of at least $6865 per individual for a no-screening early introduction approach versus screening or delayed introduction strategies.[83]

Table 2 **Cost-effectiveness of strategies for early introduction of peanut and egg***

Infant Risk Scenario	Cost Per Patient At Risk, $	QALY per Patient At Risk	Allergic Reactions Per Patient At Risk	Incremental Societal Cost to Screen, $
For peanut allergy (personal history of early onset eczema and/or egg allergy)				
No screening, early introduction	6557	19.63	0.4	—
Skin test screening before early introduction	7576	19.62	0.35	654,115,322
Specific IgE screening before early introduction	7977	19.6	0.38	911,211,774
Delayed introduction	11,708	19.46	0.72	
For peanut allergy (sibling history of peanut allergy)				
No screening before introduction	3278	19.72	0.2	—
Skin test screening with challenge before introduction	3984	19.72	0.2	Dominated
For egg allergy (early onset eczema)				
No screening, early cooked introduction	2235	19.78	0.03	—
Skin test screening before early cooked introduction	9100	19.59	0.12	2,009,351,175
Specific IgE screening before early cooked introduction	18,957	19.28	0.26	4,894,445,790
Delayed cooked introduction	10,615	19.53	0.13	

QALY = Quality adjusted life years; IgE = immunoglobulin E.
**Model simulations over 20-year time horizons; reproduced with permission from Ref. 53.*

Cost of Immunotherapy

Treating existing peanut allergy is both possible and can be highly cost-effective, although this therapy does involve a daily commitment by families and can be associated with a range of adverse effects, including anaphylaxis. Furthermore, long-term (possibly life-long) OIT may be required for ongoing benefit. A 2017 simulated cohort of children with peanut allergy found OIT to be cost-effective compared with simple avoidance, with an incremental ratio of $2142 per quality adjusted life years, and this was minimally affected when considering grocery costs, spontaneous tolerance, OIT allergic reactions, and accidental exposures.[84] A 2019 Markov model that evaluated a commercial OIT product found that this product was not cost-effective at baseline but could be cost-effective if certain assumptions were met, and a 2021 real-world study of noncommercial preschool OIT suggested cost savings could exceed $10 billion in the United States alone, with decreased rates of anaphylaxis over a longer-term horizon.[70,85]

SDM and Guideline Recommendations

SDM is a critical aspect of food allergy management, and food allergy prevention is no exception.[73,86–88] SDM is a partnership that empowers patients to engage in the decision-making process thereby increasing the odds that treatment will align with their values and preferences, while being educated about their choices, options, and the risks and benefits involved with each option.[73,88,89] SDM can help improve both the treatment decision as well as the longitudinal collaborative relationship between patients and providers.[86,89]

The changing landscape of allergy prevention guidance over the years may have sparked some degree of doubt and hesitation among patients and clinicians. Still, it is important to realize that changing guidance has resulted from the evolution of scientific evidence, with the most recent epoch of early introduction informed large randomized controlled trials with objectively defined end points of food allergy proven by oral food challenge. Each epoch has been built on knowledge and experience of the past. A critical development in contemporary studies of food allergy prevention has been clarity in trial end point (*i.e.*, challenge-proven food allergy).[90]

Food allergy prevention strategies may involve preference-sensitive choices.[45,91,92] Many current guidelines (including the NIAID guidelines) explicitly recognize the central role not only of evidence certainty but also of the patient in SDM. For example, guidelines that use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach specifically weigh the evidence certainty (*i.e.*, trial design, risk of bias, inconsistency, indirectness, imprecision, and publication bas) as well as patient considerations (*i.e.*, balance of harms and benefits, equity, feasibility, and cost-effectiveness) in each recommendation.[92,93] Although strong GRADE recommendations are favored in most circumstances and may have policy implications, conditional recommendations are more common and indicate a key role for SDM in considering the recommendation.[92,93]

There are several tools that can assist in the SDM process. Decision aids, such as the early introduction decision aid by Greenhawt[88] can be helpful to clearly describe best evidence to support options available to families. When specific decision aids are not available, the Ottawa Personal Decision Guides[94] can provide a structure for conversations with patients and have been shown to decrease decision conflict in patients and clinicians. It is important to note that SDM does not guarantee that a patient's preference will be met but rather aims to align treatment with a patient's values while also considering the best available evidence and professional expertise.

Summary

Food allergy prevention has evolved and can now be viewed as a continuum with early treatment, informed by an understanding of evidence certainty, strength of recommendations, a balance of benefits and harms, and patient preferences. The epochs of changing guidance over the decades help remind us of the importance of evidence certainty, particularly in regard to the utility of trial end points that directly reflect clinical outcomes. In addition, we must remember that humility, honesty, willingness, and open-mindedness remain powerful assets as we stand by the good and work to make it better when we can, in partnerships with our patients and their families.

Over recent decades, guidance has advised gradual loosening of restrictions on maternal and infant diets, with progressively early allergen introduction and diminishing recommendations for hydrolyzed formula. Such changes have been accompanied by advances in allergy treatment, including OIT. Although OIT is an effective treatment, SDM is central to the therapy and further research is needed to optimize management. Cost-effective care has been incorporated in GRADE guidelines to optimize value in providing food allergy care tailored to each patient and family. With insights from lessons learned, we look forward to new discoveries and the inevitable course corrections that we will encounter on the way to a better tomorrow.

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