

The Dietary Paradox in Food Allergies: Yesterday's Mistakes, Today's Evidence and Lessons for Tomorrow

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Abstract: During the last decades the prevalence of food allergy has significantly increased among children and antigen avoidance still remains the standard care for the management of this condition. Most reactions are IgE-mediated with a high risk of anaphylaxis requiring emergency medications in case of inadvertent ingestion. Recent studies showed that continuous administration of the offending food, rather than an elimination diet, could promote the development and maintenance of oral tolerance. Indeed, intestinal transit of food proteins and their interaction with gut-associated lymphoid tissue (GALT) is the essential prerequisite for oral tolerance. On the contrary, low-dose cutaneous exposure to environmental foods in children with atopic dermatitis and altered skin barrier facilitates allergic sensitization. The timing and the amount of cutaneous and oral exposure determine whether a child will have allergy or tolerance. Furthermore, previous preventive strategies such as the elimination diet during pregnancy and breastfeeding, prolonged exclusive breastfeeding and delayed weaning to solid foods did not succeed in preventing the development of food allergy. On the other hand, there could be an early narrow window of immunological opportunity to expose children to allergenic foods and induce natural tolerance. Finally, the gradual exposure to the offending food through special protocols of specific oral tolerance induction (SOTI) may be a promising approach to a proactive treatment of food allergy.

Keywords: Food allergy, avoidance, atopic dermatitis, weaning, specific oral tolerance induction.

INTRODUCTION

The prevalence of IgE-mediated food allergy in developed countries has been continuously increasing over the past 30 years [1-3]. Such an increase, involving particularly infants and toddlers, can be indirectly gathered from the increase in both the prescription of EpiPen and the number of hospitalizations for anaphylactic reactions [4,5]. Such a rapid epidemiological change cannot be justified by genetic variations, but could rather be explained by the application of public health measures for food allergy prevention based on allergen avoidance during pregnancy, breastfeeding and infancy [6]. Current knowledge suggests that a prerequisite for the development of tolerance is repeated oral exposure to food antigens [7]. In this review we analyze potential damages caused by strict avoidance used for the prevention of food allergy or for the treatment of atopic dermatitis and the possible therapeutic effect of oral food exposure. A summary of the topics discussed in this review is reported in Table 1.

FAILURE OF PUBLIC HEALTH MEASURES BASED ON FOOD AVOIDANCE

In 1980's, it was supposed that delaying the introduction of allergenic foods in infants could prevent the development of food allergy. These recommendations were developed in the absence of epidemiological data supporting such strategy and they were based on the wrong hypothesis that an early introduction of allergenic foods may be the cause of allergic sensitization. Since a significant number of allergic sensitization to food was noticed in unweaned infants [8], an avoidance policy for children at risk was established by using elimination diet in breastfeeding mothers or extensively hydrolyzed formula when breast milk was lacking [9]. Furthermore, evidence that food allergens can pass from the mother to her fetus through the placenta had been straightforwardly converted into

recommendations to avoid allergenic foods for pregnant mothers of high-risk offspring [10]. All these measures did not have any preventive effect whatsoever, but they still came to be counterproductive by avoiding the physiological interaction between food allergens and gastrointestinal mucosal immune system and preventing the development of normal regulatory mechanisms [11-13].

A key milestone on this issue has been a 2008 study [14] on the reasons of geographic variations in prevalence of the most common food allergy in the United Kingdom: the peanut allergy [15]. In this study Du Toit and his colleagues showed that Israeli Jewish children, typically weaned at 6 months of age with a peanut butter-flavored snack called Bamba, were one-tenth as likely to develop peanut allergy compared to Jewish children in the United Kingdom who were not given peanuts when they were infants in accordance with a preventive public health measure.

CUTANEOUS SENSITIZATION

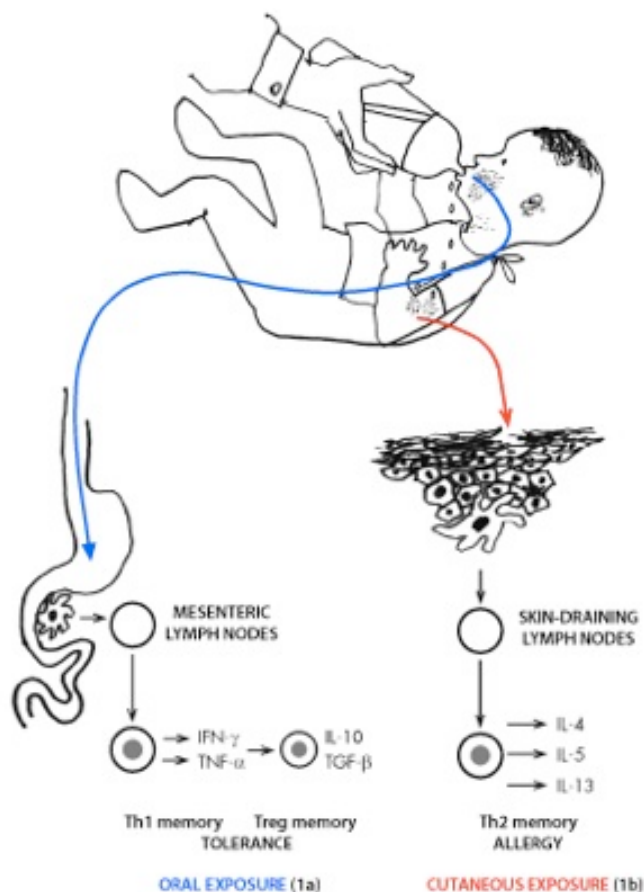
A potential explanation of the failure of strict avoidance to reduce the incidence of IgE-mediated food allergy in children has been given by the "dual allergen exposure hypothesis" according to which intestinal transit of food proteins and their interaction with gut-associated lymphoid tissue (GALT) is the essential prerequisite for the development of tolerance while the environmental exposition to low-dose food proteins through cutaneous or respiratory route leads to TH2 response and IgE production by B cells (Fig. 1) [13], [16]. Indeed, the more altered the skin barrier function is (i.e. atopic dermatitis) the earlier and stronger the food sensitization will be [17].

In children with atopic dermatitis the contact of antigens with dermal dendritic cells (Langerhans cells) is eased by inflammatory-modified skin barrier function [18-20]. In these children exclusive breastfeeding was recommended for a prolonged period and complementary feeding with allergenic foods suggested to be delayed. Until a few years ago the International Position Paper recommended that solid foods should not be introduced prior to 6 months of age, dairy products prior to one year of age, eggs before 2 years and peanuts, nuts and fish avoided for the first 3 years of life [9], [21]. Despite the lack of evidence on the correct age of introduction

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Table 1. Changing in Standard Approaches to Pediatric Food Allergy Over the Time with a Forecast for the Future Recommendations on the Basis of Current Evidences

Strategies in Facing Paediatric Food Allergy			
	Past	Present	Possible Future
Atopic dermatitis	Avoidance of highly allergic foods such as milk, eggs, fish and peanuts.	Avoidance of highly allergic foods may be tried in severe uncontrolled cases only.	No restriction diet at all.
Prevention	Restriction diet during pregnancy and lactation, delayed introduction of solid foods in the diet of infants at high risk of atopy.	No restriction diet during pregnancy and lactation; no limitation in introducing solid food beyond 4-6 months.	Supplementation of diet of pregnant women, breastfeeding mothers and infants with vitamin D and probiotics.
Therapy	Strict avoidance of the offending food.	SOTI in research setting only.	SOTI as standard treatment.
Follow-up	Food avoidance after a positive oral food challenge regardless of the amount of food that caused the allergic reaction.	Food avoidance after a positive oral food challenge regardless of the amount of food that caused the allergic reaction.	Regularly intake and gradually increments over time of the offending food starting from the last tolerated dose at oral food challenge.

**Fig. (1).** Dual-allergen exposure hypothesis. Physiological exposure to food by gastrointestinal tract elicits an immunological response that leads to tolerance. Cutaneous exposure to environmental food allergens results in allergic sensitization. Modified from Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol.* 2008; 121: 1331-6.

of potentially highly allergenic foods, the guidelines were not revised until 2008. Although the hypothesis of a cutaneous sensitization had never been considered before, today it appears easy to share: the allergenic molecules are everywhere, in the smell of the cooked food, on the hands of the parent touching the baby after having handled food, in the mother's breath one hour or more after eating [13], [22], [23], [24], [25]. The awareness of a cutaneous and inhalatory exposure to food allergens should induce us to change

our mind about prevention and treatment of food allergy [7], [13], [26]. Considering atopic dermatitis as the cause of allergic sensitization rather than the symptom is a real "Copernican Revolution". As a matter of fact recent international guidelines state that there are insufficient data to support a protective effect of any dietary intervention for the development of atopic disease in infants after 4-6 months of age [11], [27], [28].

RESTRICTION DIET IN ATOPIC DERMATITIS

The attempt of treating atopic dermatitis with a restriction diet was a major mistake that turned to be an economic burden on health services [29], [30]. It must be kept in mind that atopic dermatitis affects more than 15% of infants and that up to 90% of children with food allergy had atopic eczema in their first year of life [31]. Furthermore, the difficulties that strict avoidance implementation may have on children must be considered: from the nutritional consequences to the impaired quality of life of the affected patients and their families [32], [33]. Indeed, the economic damage that comes from keeping children on elimination diet should not be underestimated considering the costs of hydrolyzed formula or of a special diet in school cafeterias. Moreover even in highest-risk patients, atopic dermatitis is rarely induced by foods. Finally, undocumented assumptions that eczema could be caused by some foods detract from proper topical anti-inflammatory management [29]. The lack of prompt local steroid therapy coupled with the delayed introduction of potentially allergenic foods in infant diets probably plays a key role in the increased prevalence of food allergy. Unfortunately the “dietetic age” of easy diets in potentially allergic infants would be really difficult to pass over. Indeed restriction diet has become the easiest option because it is a choice that relieves of responsibilities: the introduction of potentially allergenic foods such as cow’s milk, hen eggs or peanut butter, in a infant with atopic dermatitis with probable positive skin prick test for one or more of those foods, could cause an IgE-mediated reaction.

Despite several reports on the advantages of an early introduction of allergenic foods [14], [34], [35], [36] and the lack of evidence of the benefits of avoidance in atopic dermatitis [37], it is amazing that the dietetic intervention is still being suggested by the majority of international guidelines [38], [39], [40], [41]. The NICE guidelines [41] recommend the restriction diet for infants with severe atopic dermatitis. If this were the case, the elimination diet would even more successfully improve mild to moderate atopic dermatitis. However, quite to the opposite, the utility of avoidance in atopic dermatitis has never been proven; indeed it has been denied by studies of better quality [42]. Devenney and his colleagues, conversely, successfully introduced small amounts of milk and/or egg in infants with eczema sensitized to one of those foods without getting a worsening of the eczema even when the amounts were progressively increased in order to achieve full oral tolerance [43].

AVOIDANCE OF USUALLY TAKEN FOOD

The elimination of a food from the diet after a prior ingestion with no IgE-mediated reactions could be wrong not only because it discontinues the physiological process of oral tolerance, but also because it increases the risk of anaphylaxis upon re-exposure. This event has been well reported in literature [44], [45], [46], [47] and it is probably more common than it is generally believed. To better understand the mechanism of food sensitization we reviewed the clinical records of more than 250 children older than 5 years, with very severe cow’s milk allergy, that underwent a specific oral tolerance induction (SOTI) protocol in our Institute [48]. The clinical history of these patients revealed that 46% started an elimination diet to control atopic dermatitis. Among these, at least 20% had eaten the offending food prior to elimination without any evidence of IgE-mediated symptoms (unpublished data). These data could explain the high frequency of acute reactions reported in literature at food re-exposure after an attempt to treat atopic dermatitis with oligoallergenic diet [49], [50].

Similarly, from an immunological point of view, it appears questionable that current guidelines advice to strengthen the indications to restriction diet in case of a positive food challenge, regardless of the amount of food that caused the allergic reaction. If the food oral challenge is positive but the child is able to ingest a significant amount of the offending food, full tolerance can easily be achieved by pursuing the intake of the offending food starting from

the last tolerated dose identified at the oral food challenge and then gradually increased over time. For several years and with a success rate of approximately 70%, the team of our Institute has been managing every oral food challenge in this way [51]. Even without the use of sophisticated tools for allergy diagnosis and follow-up, our grandmothers, led by common sense, would have had done the same: they would return to feed their children with very small quantities of the offending food starting from very small quantities and then, in case of no adverse reaction, would continue to feed them taking care to increase doses day by day.

THE IMPORTANCE OF EARLY COMPLEMENTARY FEEDING

Once accepted that the normal development of oral tolerance is an antigen dependent process requiring an early and repeated exposure to foods, recent studies show that delaying complementary feeding after the age of six months is not only useless, but also self-defeating in terms of sensitization to foods [35], [52], [53]. These evidences challenge the recommendation supported by the World Health Organization guidelines to exclusive breastfeeding during the first 6 months of age [54]. Those same studies have suggested the existence of a relatively narrow window of immunological opportunity to expose children to allergenic foods and induce tolerance in a natural way. The tolerance window probably ranges between 3-4 months to 6-7 months [55]. Nevertheless, even the earliest food exposures, since birth, do not increase the risk of IgE-mediated sensitization [34], [56], but rather seem to increase the risk of food related diseases mediated by different pathogenetic way, such as FPIES, celiac disease and diabetes [57], [58], [59].

Starting on these assumptions, some randomized controlled trials (RCTs) are currently in progress to evaluate whether early introduction of allergenic foods may lead to tolerance and protect against the development of IgE mediated food allergy. The most important studies are the LEAP study (Learning Early About Peanut Allergy) [60] and the EAT study (Enquiring About Tolerance) [61]. The LEAP study is analyzing the preventive effect of an early introduction of peanuts and it will reach completion in 2013. The EAT study is investigating the effect of the introduction of six allergenic foods (peanut, cow’s milk, hen egg, fish, wheat, and sesame) from three months of age joint to breastfeeding. The results of the EAT study will be analyzed and published in 2015. Even today, however, current evidences suggest that, particularly in high-risk children, complementary feeding should not be started too late, possibly before six months of age alongside continued breastfeeding. Furthermore, the breastfeeding mother should no longer not be subject to unnecessary dietary restrictions [62]. Indeed breast milk is rich of factors that promote the acquisition of food tolerance such as secretory specific IgA and tolerogenic interleukins (IL-10 and TGF-beta) [63], [64], [65].

THERAPEUTIC EXPOSURE TO ALLERGEN: SPECIFIC ORAL TOLERANCE INDUCTION (SOTI)

Specific oral tolerance induction (SOTI), the gradual monitored administration of an allergen over months and years for the purpose of treatment is another example of the importance of antigen exposure through gastrointestinal section to allow the development of tolerance. Small antigen doses induce an antigen-specific suppression by regulatory T-cells cytokines IL-10 and TGF-beta in Peyer’s patches, while high antigen doses induce anergy or clonal deletion of T-cells [66], [67].

Several studies have shown encouraging results in SOTI with milk [48], [68], [69], [70], egg [69], [70], [71] and peanut [72], [73] as treatments for food allergy. Nevertheless this approach is not yet considered ready for community recommendations [74]. The main criticism expressed by avoidance supporters is that the benefits of SOTI have not been measured in largely subjective outcomes (i.e. enhancement or worsening of quality of life with validate instru-

ments) and may be counterbalanced by serious adverse effects [74], [75]. Indeed adverse reactions are common and largely unpredictable during the SOTI protocol, with several systemic reactions occurring at previously tolerated doses, often in the setting of exercise or during a viral illness [76], [77]. Despite this, fatal reactions have not been reported in both rush phases and in very severe food allergy and only one case of near fatal asthma during a unique rapid rush phase of desensitization to milk has been described [78], [79]. Finally, avoidance is not a risk-free option: reports of accidental exposure to allergic reactions are common. Half of the children with IgE-mediated food allergy experience accidental ingestion of the allergen within 5 years, while 75% experience accidental ingestion until 10 years of age [74], [80]. For this reason and in order to fight accidental ingestions, allergic children should always be provided with emergency medications at close hand.

A further controversial aspect of SOTI is its potential desensitizing role without necessarily promoting an ongoing tolerance. According to a few studies it seems that tolerance depends on regular intake. A significant number of successfully desensitized children partially lost their tolerance after a brief period (weeks-few months) of a secondary elimination diet [70], [81]. This could be important for "tasty food" allergies not present in an everyday diet, but it is not the same for most common foods such as wheat, milk and eggs, which cannot be easily avoided.

CONCLUSION

Food allergy is an increasingly prevalent disorder and a health burden in developed countries. Delayed weaning and prolonged exclusive breastfeeding as well as other strategies based on avoidance of solid foods have proved to be ineffective and probably harmful. Over the past few years new data that challenge many old dogmas about allergies have been published. The prerequisite for the development of tolerance is repeated oral exposure to antigen while avoidance prevents the development of normal regulatory mechanism. No evidence of a preventive effect of the maternal diet during pregnancy or lactation was documented. There were no consistent findings regarding the role of dietary restrictions in young children with atopic dermatitis. In children with an altered skin barrier function sensitization occurs through cutaneous exposure to low dose environmental foods before the same foods are introduced in the child's diet. Indeed, current evidences allow to assert that complementary feeding should be started before six months of age alongside continued breastfeeding, particularly in high-risk children. In infants with an atopic constitution, sensitization to foods, particularly milk and eggs, usually begins during the first year of life before these foods are introduced into the diet. In the majority of cases, if these are not introduced, sensitization reaches its peak during the 2nd or 3rd year of age [82]. Recommendations that increase the risk of food allergy such as the common habit to remove a food from the diet of an atopic child after a prior ingestion without acute IgE-mediated symptoms should be abandoned. Indeed, this is not effective in controlling the eczema and could lead to an increased risk of anaphylaxis upon re-exposure to the offending food after a period of elimination.

ABBREVIATIONS

GALT	=	Gut-associated lymphoid tissue
SOTI	=	Specific oral tolerance induction
FPIES	=	Food protein induced enterocolitis syndrome
LEAP	=	Learning early about peanut allergy
EAT	=	Enquiring about tolerance
RCTs	=	Randomized controlled trials
NICE	=	National institute for health and clinical excellence
OFC	=	Oral food challenge

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CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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