

Food allergy and atopic dermatitis: Prediction, progression, and prevention

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Abstract

The rising burden of allergic diseases in childhood requires a compelling need to identify individuals at risk for atopy very early in life or even predict the onset of food allergy and atopic dermatitis since pregnancy. The development and clinical phenotypes of atopic diseases in childhood depend on a complex interaction between genetic and environmental factors, such as allergen exposure, air pollution, and infections. Preventive strategies may include avoidance measures, diet supplements, and early complementary food introduction. Overall, the management of allergic diseases has been improving to date toward a patient's tailored approach. This review will cover the current understanding of risk factors, prediction, and management of food allergy and atopic dermatitis in childhood and discuss how these may contribute to the modification of the natural history of food allergy and atopic dermatitis.

KEYWORDS

allergy, atopic dermatitis, childhood, diagnostics, eczema, evolution, food allergy, management, pediatric, prevention, risk factors, treatment

1 | INTRODUCTION

Allergic diseases typically manifest in infancy, with the so-called atopic march, generally beginning with the development of IgE antibodies to food allergens, accompanied by symptoms of atopic dermatitis (AD) and food allergy (FA), followed by the occurrence of allergic rhinitis and asthma at school age.¹ A progression from cow's milk and/or egg allergy in early infancy to additional class I food allergies, for example, peanut, is common. The onset of pollen allergy then offers yet more opportunity to develop class II food allergies, that is, the pollen-food syndrome (PFS) (Figure 1).² The prevalence of allergic diseases, including AD and FA, has rapidly increased in recent decades, particularly in affluent societies, affecting up to one-third of the population.³ In

the United States from 1999 to 2011, the prevalence of reported allergic skin diseases (AD) among children increased by 70% and that of reported FA by 50%.⁴ However, it should be considered that only one-third of reported food hypersensitivity is confirmed by oral food challenge (OFC) at 10 years of age.⁵ Accordingly, a systematic review described a 10-fold difference between self-reported and challenge-verified prevalence of FA in childhood.⁶ Besides similar time of onset, FA and AD may be linked by a causal relation. Furthermore, an altered immune response is involved in both FA and AD. The immune deviation has an important genetic component,⁷ even if the recent increase of FA and AD suggests that is mainly due to changes in epigenome driven by environmental exposure.⁸ Environmental factors possibly involved comprise: (i) reduced exposure to beneficial microbes and bacterial metabolic products, as result of urban living in Western lifestyle ("hygiene hypothesis"); (ii) routes and burden of food allergen exposure; (iii) changes in diet (obesity); and (iv) nutrients. End-organ dysfunction at epidermal epithelial in AD may play a pathogenetic role too. This review attempts to analyze the recent advances in prediction, progression, and prevention of AD and FA.

Abbreviations: AD, Atopic dermatitis; BT, Basal tryptase; EE, Blood eosinophils; CS, Cesarean section; CMA, Cow's milk allergy; EPIT, Epicutaneous immunotherapy; FA, Food allergy; HMGB1, High-mobility box 1; LCPUFA, Long-chain polyunsaturated fatty acid; OIT, Oral immunotherapy; OFC, Oral food challenge; PIBD, Pediatric inflammatory bowel disease; PFS, Pollen-food syndrome; QoL, Quality of life; SPT, Skin prick tests; SLIT, Sublingual immunotherapy; Th1, T helper 1; Th2, T helper 2; TEWL, Transepidermal water loss.

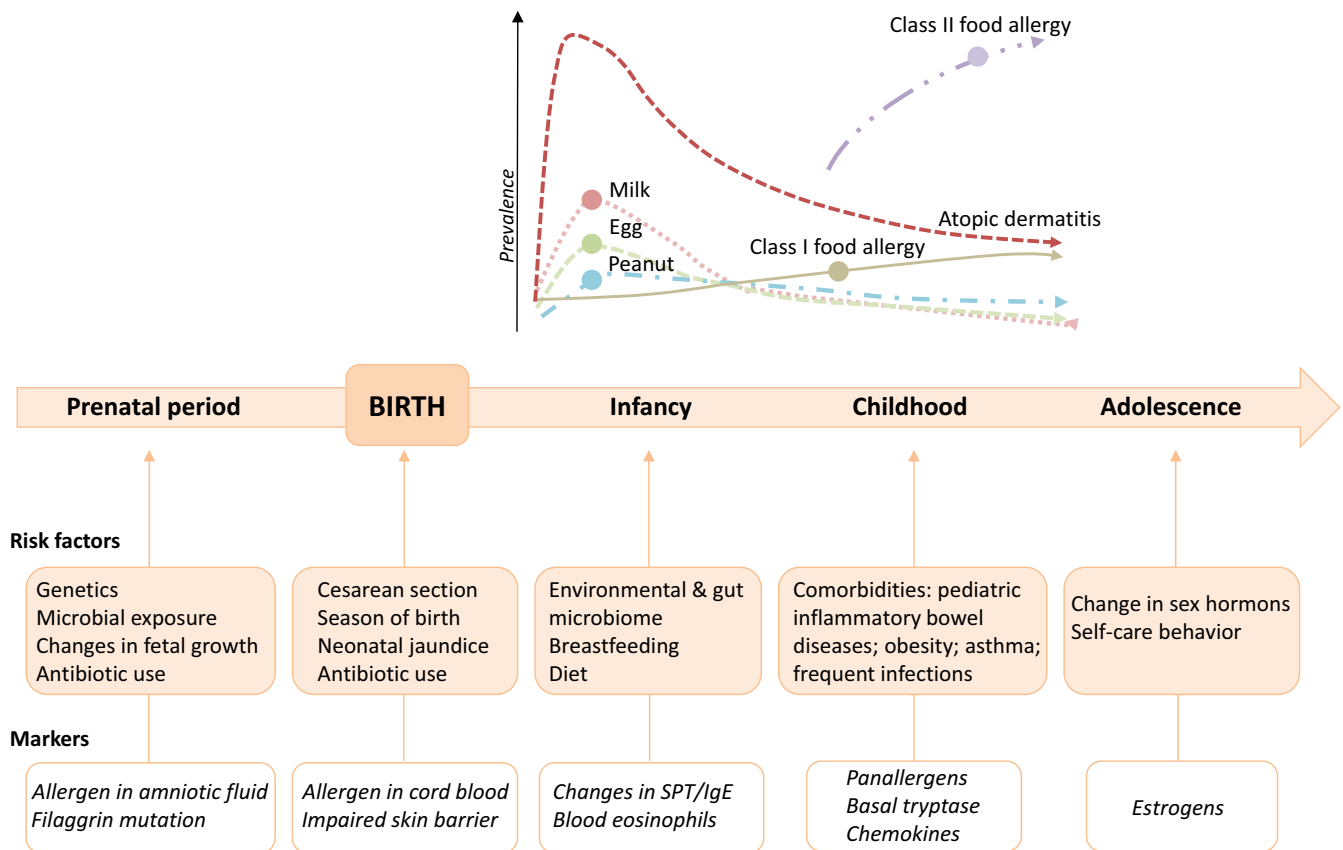


FIGURE 1 Timeline of the development of atopic dermatitis, class I and class II food allergies, with their risk factors and relevant markers under investigation (In part modified by Du Toit et al. 2009) [Colour figure can be viewed at wileyonlinelibrary.com]

2 | PRENATAL RISK FACTORS

During gestation, the immunologic environment of the fetus is T helper 2 (Th2) predominant to be protected from rejection. After birth, the Th2 skewing persists for some months before the immune system gradually changes toward a T helper 1 (Th1) immune response.⁹ Environmental factors may alter immune development in pregnancy. This is supported by findings that food sensitization in the offspring is augmented by exposure to pollen during gestation.¹⁰ It has been shown that common food allergens cross the placenta as they were detected in amniotic fluid samples from pregnant women at 15–20 weeks of gestation and from 20 women after delivery as tested by antibody microarray.¹¹ Furthermore, 9 of 37 newborns with positive IgE to ovalbumin in cord blood developed egg allergy or AD at 14 months of age.¹² Intervention studies reported that avoiding allergenic foods in pregnancy does not reduce the risk of atopy.¹³ Accordingly, observational studies supported the hypothesis that low consumption of peanut, tree nuts, or cow's milk in pregnancy, particularly among non-allergic women, may possibly increase the risk of developing allergy to peanut, tree nuts,¹⁴ and cow's milk,¹⁵ respectively. Moreover, low maternal wheat intake was a risk factor for AD onset.¹⁴

It has been postulated that limited microbial exposure and perturbations in growth and composition of intestinal microbiota early in pregnancy (such as antibiotics, dietary habits, and other lifestyle influences) contribute to an increased incidence and severity of allergic

disorders.¹⁶ In utero exposure of bacterial patterns primes the immune system and/or the epithelium to respond appropriately to pathogens and commensals after birth. Accordingly, a meta-analysis suggested that antibiotic exposure during the last two trimesters of pregnancy increases the risk of wheeze/asthma in childhood (age ≥ 3 years).¹⁷ Therefore, prenatal intervention studies on the role of microbiome for the onset of FA and AD are lacking.

Regarding other risk factors for AD, obesity, or vitamin D levels in pregnancy were discussed, recently. Accelerated growth and a relative increase in abdominal circumference between the first and second trimesters of pregnancy were associated with a higher risk for AD.¹⁸ Conversely, a Saudi Arabian birth cohort study found that decreased fetal abdominal circumference was linked to AD in the first 2 years.¹⁹ These contrasting findings suggest a potential link between fetal growth trajectory during the second half of pregnancy and the development of allergy. A likely reason may be the maternal obesity that represents a key factor for the modulation of neonatal immune system development.²⁰ Furthermore, a modest association between low vitamin D levels and increased risk of childhood AD in the offspring was found in a meta-analysis.²¹ Particularly, low maternal 25-hydroxyvitamin D levels were linked to an increased risk of allergic sensitization, early childhood AD, and asthma in a Taiwanese pediatric study.²² Conversely, no association between levels of 25-hydroxyvitamin D (in mid-gestation and at birth) and the risk of AD was found among children from Generation R Study until 4 years

of age.²³ Despite a growing number of studies investigating the relationship between maternal vitamin D status during pregnancy and childhood allergic outcomes, the epidemiological evidence remains insufficient to provide clinical guidance. The role of n-3 long-chain polyunsaturated fatty acids (LCPUFAs) in preventing allergy has been a topic of investigation. There has been an increase in the ratio of dietary n-6 LCPUFAs/n-3 LCPUFAs in Western countries. This is suspected to be involved in the allergy epidemic, as n-3 LCPUFAs have anti-inflammatory effects, in contrast with n-6 LCPUFAs. However, contrasting data have been reported on the role of fish intake and n-3 LCPUFAs during pregnancy on the development of AD and FA.⁸

3 | PERINATAL INFLUENCES

Perinatal analyses, including type of delivery, antibiotics, season of birth, and neonatal jaundice, have been evaluated on the risk of allergic diseases.¹⁸ Delivery by cesarean section (CS) may predispose the development of FA in early childhood presumably due to the lack of exposure to vaginal and perianal bacteria. A prospective Greek birth cohort study showed that children born by CS had a threefold higher probability of FA in the first 3 years of life, especially those with allergic predisposition.²⁴ No effect was shown on the risk of AD, in agreement with previous findings.¹⁸ Along this line, as antibiotics are frequently prescribed during the neonatal period among preterm infants, an antibiotic-induced delay in intestinal bacterial colonization may increase the risk for developing allergic disorders.²⁵ A relationship between the autumn-winter season of birth and early onset of FA has been reported by a multicentre cross-sectional study.²⁶ Although the reason for "season-of-birth effect" on the frequency of atopic diseases has not been fully elucidated yet, the amount of solar radiation immediately after birth might be crucial. Actually, among children born in autumn-winter, the average solar radiation in the first 3 months of life showed a strong negative correlation with the sensitization to egg, milk, and wheat before 6 months.²⁷ Moreover, seasonality influenced the risk of AD in a Danish nationwide cohort study, with the highest risk occurring in children born during fall and the lowest risk in those born during spring.²⁸ This effect can be explained by a transcutaneous allergen exposure and dry skin in the winter season. This cohort study showed also that neonatal jaundice was a weak but significant risk factor for childhood AD.²⁸ Accordingly, neonatal jaundice was associated with the development of allergic diseases, mostly allergic rhinitis and AD, in a population-based study.²⁹ Furthermore, this risk was linked with high bilirubin levels requiring phototherapy.³⁰ The pathophysiology of the relationship between neonatal jaundice and allergic consequences remains unclear and warrants further exploration. The key role of a compromised barrier of neonatal skin as predisposing factor in the development of childhood AD has recently been demonstrated. A defect in skin barrier function, as increased transepidermal water loss (TEWL), determined at birth and at 2 months of age was significantly predictive of AD at 12 months in a large birth cohort study.³¹ These changes were seen in both

high-risk and low-risk infants and, crucially, were independent of filaggrin loss-of-function mutations. Accordingly, a lowest quartile TEWL at birth was protective against AD. The mechanistic implications would be that defects in skin barrier function may facilitate allergen entry and immune priming.

4 | POSTNATAL EXPOSURES

In infancy, important risk factors for FA and AD are altered microbiome and exposure to food allergens. Accumulating evidence suggests that microbial environment plays a significant role in the pathogenesis of allergic diseases.³² Changes of the resident microbiome, with production of protective metabolites, such as short-chain fatty acids, tryptophan, or zwitterionic polysaccharides can have defensive effects against allergic diseases through diet, siblings, daycare, dogs, or farming environments. This microbial diversity might be necessary to instruct a well-adapted immune response and regulated inflammatory responses to other inhaled and ingested environmental elements, such as allergens, particles, and viruses.³³ Rapid environmental transition and modern lifestyles are likely driving changes in the biodiversity of the human microbiota.³⁴ Qualitative and quantitative alterations in the gastrointestinal microbiota, early and massive source of microbial exposure, might underlie the allergy epidemics.³⁵ Regarding FA, gut microbiota composition and an elevated *Enterobacteriaceae/Bacteroidaceae* ratio in early infancy were associated with food sensitization at 1 year of age.³⁶ Correspondingly, food-sensitized children exhibited lower diversity of both, total microbiota and bacterial phylum *Bacteroidetes*, with an increased number of *Firmicutes* compared with healthy children.³⁷ Alterations in bacterial taxa seem to be associated with a particular type of FA. Infants with cow's milk allergy (CMA) have higher anaerobic bacteria,³⁸ *Ruminococcaceae*, *Lachnospiraceae*³⁹ and those allergic to peanuts higher *Bacteroides*.⁴⁰ Strong evidence has been achieved that exposure to farm environment and cowshed-associated bacterial flora protects from the development of allergic airway diseases in childhood.⁴¹ Similar studies are needed to identify the skin microbiome and understand how bacteria might alter immune response in AD.

It has been hypothesized that early sensitization to food allergens might be due to their ingestion through breastmilk, explaining reactions to foods never consumed before.⁴² A homemade microarray with antibodies against ten major food allergens and panallergens was incubated with breastmilk from 14 Spanish women. All allergens studied were detected with a wide variation in protein concentration in breastmilk, probably due to different food ingestion from mothers' diet. In particular, also the most potent peanut allergen Ara h 2 was detected in breastmilk samples.⁴³ So, breastfeeding may be a gateway of IgE sensitization to foods due to the ingestion of allergens dissolved in maternal milk. These results on the first allergenic contact are important as they might condition the future of the allergic state of the child regarding both induction of sensitization/allergy and tolerance. However, it should be noted that avoiding cow's milk and egg during

lactation did not prevent food sensitization in the offspring, while the effect on AD was unclear.¹³

Further critical environmental exposures in urban setting have been implicated with the explosion of AD, such as house dust mite and cockroach antigen exposure, as well as forced indoor heating and excessive cleaning. Pollutants themselves in conjunction with climate factors have a great impact on prevalence and severity of AD.⁴⁴ On the other hand, a lower UVB exposure could have contributed to the increased AD incidence among industrialized countries.⁴⁵ This observation can be partially explained by a reduced exposure to solar irradiation in children living in the urban settings because of less time spent outdoors and decreased sun exposure by smog and surrounding structures.

5 | BIOMARKERS OF DISEASE SEVERITY

Early biomarkers able to distinguish different phenotypes of allergic diseases have been studied, such as high-mobility box 1 (HMGB1) for AD and serum basal tryptase (BT), blood eosinophils (EE), and chemokine CCL17 for FA. The HMGB1, an inflammatory marker belonging to the alarmin family, was well correlated with the AD severity, as well as with comorbidities (allergic rhinitis and asthma), although it was not related to the allergic sensitization.⁴⁶ Additionally, IL-17/IL-23 axis and IL-10 levels were linked to HMGB1, suggesting their role in inflammatory responses of the skin, as previously suggested in animal models.⁴⁷ Serum BT levels in children presenting FA were a risk factor for severe systemic reactions.⁴⁸ Moreover, assessing the difference between reaction and post-reaction tryptase levels may improve diagnostic sensitivity. On the contrary, BT did not play any diagnostic role in children with drug hypersensitivity.⁴⁹ Supporting previous observations that EE had reflected the present atopic status,⁵⁰ elevated EE at 4 weeks of age had a predictive value for the onset of AD at 7 months, 1, 2, and 3 years of age in a birth cohort with high risk for atopy.⁵¹ The chemokine CCL17 has been reported to correlate with the disease severity in infants suffering from AD sensitized against food or airborne allergens.⁵² Interestingly, this correlation was higher for patients sensitized to food allergens and CCL17 was found mainly in the (inflamed) skin but not in the gut. Moreover, among infants with AD and food sensitization, the detection of high levels of CCL25, ligand of CCR9, localized primarily in the gastrointestinal tract, could suggest the impact of CCL17 on food allergen-induced inflammation processes.

Clinical entities due to IgE sensitization to cross-reactive aeroallergens and food allergens are described for many sources of plant origin (PFS), fungal origin (*Alternaria*-spinach syndrome), and invertebrate, mammalian, or avian origin (mite-shrimp, cat-pork, and bird-egg syndromes).⁵³ IgE cross-reactivity is a phenomenon of IgE antibody recognizing, binding, and inducing an immune response to homolog allergens. Cross-reactivity often occurs between allergenic molecules in closely related species, or well-preserved molecules belonging to the same protein family present in widely different species.^{54,55} PFS is a class II FA as consequence of sensitization to cross-reactive

aeroallergens that occurs from pre-school age on.⁵⁶ The use of component-resolved diagnostics facilitates the understanding of PFS, leading to a new classification based on panallergen IgE sensitization profiles.⁵⁷ Moreover, the IgE sensitization to panallergens can be used as predictor for cross-reactive allergy and as biomarker for disease severity.⁵⁸

6 | NATURAL HISTORY

New information on the natural history of FA has been recently provided. A study on a birth cohort born on the Isle of Wight⁵⁹ confirmed that a large number of children outgrew cow's milk and egg allergy by 10 years of age, while the prevalence of peanut allergy appeared to be stable during the first 10 years of life.^{5,60} Between the age of 3-10 years, only approximately 10% of children outgrew their peanut allergy.⁵⁹ Differently, in the Australian prospective HealthNuts study, 22% of children with peanut allergy at 1 year of age reached tolerance to peanut at 4 years.⁶¹

Most children with cow's milk or egg allergy develop tolerance over time, but the onset of its acquisition varies considerably. Tolerance development should be assessed regularly by OFC, and several periodical OFCs may be required. So, simple markers identifying the development of food tolerance in childhood are urgently needed. The usefulness of skin prick tests (SPT) in predicting the loss of clinical egg hypersensitivity has been studied. An Italian study showed that the negative conversion of a positive SPT over time was indicative of egg tolerance, compared with positive SPT persistence.⁶² In a Danish pediatric population, a decrease of IgE to egg white and to ovomucoid was associated with the acquisition of egg tolerance.⁶³ Conversely, in all cases with increased levels of IgE to ovomucoid, the rechallenge was positive. Therefore, the conversion of positive egg SPT or the decrease of specific IgE may provide useful information to identify children who acquire tolerance to egg and it may reduce the need of OFCs. On the other hand, patch tests in FA do not have a diagnostic value, particularly with egg and cow's milk.⁶⁴ Although numerous attempts have been made to determine the diagnostic cutoff of specific IgE and SPT for egg allergy, no cutoff value by itself may allow a firm diagnosis of raw, heated, or baked egg allergy.⁶⁵ Children with IgE-mediated hen's egg allergy often tolerate baked egg within a wheat matrix.⁶⁶ A prolonged and extensive heating increased tolerance toward egg proteins also without wheat matrix among children.⁶⁷ Moreover, even though tolerance should always be assessed by an OFC, it could be supported by a negative prick to prick with baked egg products.

Finally, understanding the natural history of food sensitization beyond early childhood may be useful to predict adolescent FA. Skin sensitization to cow's milk, hen's egg, and peanut at 12 months of age was associated with increased risk of adolescent sensitization and probable FA at 12 and 18 years among subjects from an Australian birth cohort.⁶⁸ A collective body of evidence suggests a progression from AD and FA to wheezing, asthma, and sensitization to inhalant allergens at school age.^{69,70} Dietary intake in early life combined with atopy history may have an impact on the risk of developing asthma.

In particular, milk restriction due to CMA significantly increased and mediated the association between food consumption and the risk of childhood asthma.⁷¹ On the other hand, a dietary restriction during infancy, in particular cow's milk, may influence later eating behavior and food preferences.⁷² An early and appropriate dietetic intervention is therefore important to monitor both the exclusion and reintroduction period. Moreover, the progression of FA may be linked to other inflammatory diseases. CMA in infancy has been linked with subsequent development of pediatric inflammatory bowel disease (PIBD) and asthma in a Finnish nationwide birth cohort.⁷³ The use of antibiotics during the first 12 months was associated with symptoms suggestive of CMA, proposing a role of intestinal microbiota in the disease pathogenesis, as also described for PIBD⁷⁴ and asthma.⁷⁵ Logically, children with CMA were more likely to develop asthma accordingly to the "atopic march" hypothesis. Moreover, it may be speculated that sometimes the infant CMA digestive symptoms may represent early signs of PIBD.⁷³ It is also possible that dietary modification due to CMA may influence the gut microbiome and immune responses and favor the development of PIBD among genetically predisposed infants.

Allergic diseases exhibit sex differences, and there is mounting clinical and animal model evidence that implicates sex hormones, particularly estrogen, in being key mediators of these differences.⁷⁶ Virtually all atopic diseases affect boys more than girls in childhood. The onset of puberty, however, reverses that trend for most allergic disorders. Survey studies collectively suggest that estrogen levels correlate with symptom severity and likely contribute to the increase of allergic diseases in adult female.⁷⁷

7 | PREVENTION STRATEGIES

Strategies to prevent AD and FA have focused on limiting exposure to potential allergens, early introduction of complementary foods, supplementing diet with probiotics, and unsaturated fatty acids.⁷⁸ As dust mites may play a role in the pathophysiology of AD, avoidance strategies have been evaluated to reduce the risk of developing AD in high-risk infants compared to randomized controls.⁷⁹ However, at the moment, it is not possible to determine clear implications from the very low-quality evidence currently available and dust mite avoidance should not be recommended for this purpose.⁸⁰ There has been a long-standing debate on allergy prevention by reducing or increasing exposure to food allergens, delaying or advancing weaning. Current evidence does not show that AD and FA incidence is lower in breastfed infants.^{81,82} Nonetheless, breastfeeding remains the cornerstone of infants' nutrition program as it is beneficial for growth and immune maturation and it is recommended for at least 6 months. Besides, prolonged exclusive breastfeeding is not protective on the development of AD.⁸³ Delaying the introduction of solid foods until later than recommended minimum weaning age failed to show a preventive effect toward allergy in infants at high or normal risk.⁸⁴ On the other hand, early introduction of 6 allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat) from 3 months of age has not been proven to prevent allergic diseases at 1 and 3 years of

age in general population.⁸⁵ Recently, a protective effect against the development of peanut allergy has been shown introducing peanuts from 4 to 11 months of age among high-risk children.⁸⁶ In the 5-year follow-up, peanut consumption was continued and tolerance was sustained, even after 1 subsequent year of avoidance.⁸⁷ Further detailed recommendations of introduction of peanuts into the diet have been summarized by an expert panel.⁸⁸ Additional studies for other foods are needed. Overall, the best way forward for the general population would be starting the weaning at 4-6 months with a progressive step-wise introduction of all foods, including allergenic ones within a few months, in infants at both, low and high risk for allergy.⁸⁹

The prevention of allergic diseases is exploring possible strategies for correcting dysbiosis and enhancing exposure to beneficial microbes.⁹⁰ From this perspective, probiotics, acting as promoters of an adequate balance in the gut microbiota,⁹¹ have been suggested as intervention to prevent allergic diseases.⁹² A meta-analysis of 16 studies showed that probiotics' administration was protective against the development of AD, only when administered sequentially during pregnancy and then after birth to high-risk and normal-risk infants, in particular *Lactobacillus rhamnosus* GG alone and combined with *Bifidobacterium*.⁹³ Therefore, the use of probiotics for pregnant and breastfeeding women, and infants at high risk of developing allergies is recommended by a World Allergy Organization panel, although evidence level is still low.⁹⁴ Also an Italian metanalysis estimated that infants treated with probiotics had a significantly lower risk ratio for AD compared with controls, especially those supplemented with a mixture of probiotics.⁹⁵

A systematic review found limited evidence that n-3 LCPUFAs supplementation in pregnancy and/or during breastfeeding prevents allergy.⁹⁶ However, a recent prospective study⁹⁷ showed that n-3 LCPUFAs supplementation from docosahexaenoic acid and arachidonic acid during infancy may reduce the risk of skin and respiratory allergic diseases in childhood.

8 | THERAPEUTIC APPROACHES

At present, the cornerstone for management of FA is represented by avoidance measures. Difficulties in avoiding responsible food allergens may result in accidental exposure and the risk of triggering severe clinical reactions. Pharmacological therapies are available to help people manage symptoms when they are exposed to food allergens. Patients at risk of anaphylaxis or who have experienced anaphylaxis should have an epinephrine auto-injector and should be educated when and how to use it.⁹⁸ However, lack of adherence to recommended treatment and self-care is high, particularly among adolescents with FA.⁹⁹ Interventions improving provision and utilization of management plans could address patients' perception of the severity of anaphylaxis and facilitate good adherence behaviors.¹⁰⁰ Besides, training programs are needed for teachers and caregivers to develop confidence in their ability to care for food-allergic children.¹⁰¹

Long-term management of FA involves taking ongoing treatment to prevent symptoms from reappearing or worsening and dietary

interventions. Oral immunotherapy (OIT) represents a significant focus of treatment for FA, inducing desensitization and tolerance.¹⁰² The mechanisms of this tolerance induction include the active modulation of the immune response to promote regulatory T-cell development and immunologic skewing away from a Th2 response.¹⁰³ Although OIT has shown potential as treatment, it has been limited by heterogeneous clinical responses, high rates of adverse reactions, and potential for loss of protection with cessation of therapy. Adverse effects of OIT are often mild and self-limited; nevertheless, the use of adrenalin is not infrequent.¹⁰⁴ Different strategies have been proposed to improve the safety of OIT, including alternative routes of exposure (sublingual, epicutaneous), adjuvants for immunotherapy (anti-IgE, probiotics), as well as biomarkers of safe and successful treatment.¹⁰⁵ However, a successful OIT is not always strictly related to a positive impact on children's quality of life (QoL). A recent study reported that parents perceived limited benefit from the child undergoing egg OIT; interestingly, the improvement in health-related QoL was inversely associated with the frequency of OIT-related reactions, suggesting that if safety is compromised, QoL does not improve.¹⁰⁶ Similarly, health-related QoL changes were not statistically different after a double-blind placebo-controlled OFC with cashew nut among children participating in a clinical trial.¹⁰⁷ Discordances have been found in a study examining changes in QoL of children with FA during the up dosing phase of OIT with improvement in 35%-50% of patients, but deterioration in 25%-30%.¹⁰⁸ Certainly, a lower maximal tolerated dose during OIT induction is associated with worse indices of QoL primarily in children.¹⁰⁹ Consequently, if the outcome of OFC or desensitization protocol does not change children's diet, and the fear for accidental exposure does not drive the need for accurate diagnosis, and then part of the beneficial effect of the food reintroduction might be lacking.¹¹⁰

Different mucosal-targeted immunotherapeutic approaches, such as sublingual immunotherapy (SLIT), have shown promising results. A randomized, double-blind, placebo-controlled trial on peanut SLIT induced a modest level of desensitization, decreased immunologic activity over 3 years in responders, and excellent long-term safety profile.¹¹¹ No severe symptoms or use of epinephrine was observed, although a high rate of patients (>50%) discontinued therapy. Comparing safety and efficacy of OIT and SLIT for the treatment of peanut allergy, OIT appeared far more effective than SLIT but associated with more adverse reactions and early study withdrawal.¹¹² In a small minority of subjects, sustained unresponsiveness was seen after 4 weeks of avoidance, with suppression of basophil effector cell function and dendritic cell-driven Th2 cytokine responses after peanut OIT, and some reversibility of those responses when antigen was discontinued.¹¹²

Epicutaneous immunotherapy (EPIT) involves the application of a patch containing the food allergen to intact skin with aiming to suppress allergic inflammation.¹¹³ Preclinical studies indicate that EPIT decreased the clinical and allergen-specific Th2 responses, and increased local and peripheral Foxp3+ Tregs.¹¹⁴ Phase 1 and phase 2 clinical studies recently showed safety and high adherence of peanut EPIT. After 52 weeks of treatment, a multicentre, randomized, controlled trial demonstrated a statistically significant effect, with a great

increase in success dose at OFC.¹¹⁵ The highest responses were reported among younger children. Clinical outcome, high adherence and significant changes in immune pathways support further investigation of this novel therapy.

Anti-IgE monoclonal antibody (omalizumab) has been also proposed to reduce OIT-induced allergic reactions. A protocol of omalizumab-assisted OIT among egg- and cow's milk-allergic patients refractory to conventional OIT showed that all patients achieved complete desensitization with the occurrence of mild allergic reactions during the induction phase of OIT only in 4 patients.¹¹⁶ However, 60% of patients with cow's milk OIT and 33% of patients with egg white OIT relapsed with decreased clinical reactivity threshold at 2-4 months after suspending omalizumab. The different type of food used among studies may be significant, as it has been suggested desensitization with cow's milk was better tolerated as compared to egg.¹¹⁷ Interestingly, outcomes of efficacy were not improved in a randomized double-blinded placebo-controlled trial of omalizumab in combination with cow's milk OIT.¹¹⁸ On the other hand, adverse reactions were markedly reduced during OIT escalation in subjects treated with omalizumab. Further investigations are needed to test a longer maintenance therapy with omalizumab. A recent study addressed the potential of probiotics to induce beneficial gut immune modulation in association with peanut OIT showing higher tolerance rates after stopping it.¹¹⁹ However, definitive conclusions cannot be drawn, because a control group receiving OIT without probiotics was not included. Prediction of the effects before or at early phase of OIT would be important to increase safety and efficacy, for example, changes in allergen-specific antibodies. Regarding egg OIT-induced changes in serum allergen-specific IgG subclasses and IgA levels, a good response to OIT was associated with significant increases in IgG1 levels after rush phase and high baseline IgA levels, compared with small deviations in low responders.¹²⁰ These changes in IgG1 and IgA levels could be potentially useful biomarkers to predict positive clinical response to OIT. Although the effects of desensitization have been conclusively shown, it is currently unknown whether clinical protection persists after stopping therapy. A sustained unresponsiveness was demonstrated in half of subjects treated for up to 5 years after stopping peanut OIT.¹²¹ OIT favorably modified the peanut-specific immune response in all subjects completing the protocol. In particular, smaller SPT results and lower allergen-specific IgE levels were predictive of successful outcome. Moreover, a sustained unresponsiveness after egg OIT was enhanced with longer duration of therapy and increased the likelihood of tolerating unbaked egg in the diet.¹²² On the contrary, peanut OIT and SLIT induced rapid suppression of basophil effector functions, dendritic cells activation, and Th2 cytokine responses during the initial phases of immunotherapy in an antigen-non-specific manner.¹²³ Although there was some interindividual variation, immunotherapy effects appeared to be temporary in many patients.

The management of AD requires a complex approach.¹²⁴ Triggering factors such as foods should be avoided and superinfections treated. Emollients able to repair skin barrier and cleaners free of preservatives and perfumes are recommended. When topical corticosteroids do not control the disease, several options are available including topical

inhibitors of calcineurin,¹²⁵ wet-wrap dressing and as third-line phototherapy, systemic corticosteroids, or immunosuppressant (cyclosporine, azathioprine, methotrexate). The usefulness of antihistamines, probiotics, and allergen immunotherapy is debated. Whatever measure is chosen, optimal treatment of AD requires strategies of patient empowerment for self-responsible handling of episodic aggravation. Therapeutic patient education programs give significant benefit for the families and the individually tailored single nurse consultation is recommended in addition to medical care.¹²⁶

9 | CONCLUSIONS

Several exciting advances in our understanding of FA and AD in childhood have been reached in recent years. In addition to the known genetic predisposition, the dominant risk factors for allergic diseases are represented in environmental trigger, particularly from urban settings. The rising burden of allergic diseases drives effort to identify individuals at risk for atopy very early in life or even predict their development since pregnancy. Overall, the management of FA and AD has been improving to date toward a patient's tailored approach. Further studies will be helpful to consolidate our knowledge about the promising preventing and therapeutic strategies with novel perspectives in the management of allergic diseases.

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