



REVIEW ARTICLE

WILEY

Epicutaneous sensitization to food allergens in atopic dermatitis: What do we know?

Elizabeth Huiwen Tham MMed, MCI^{1,2} | Mohana Rajakulendran MMed, MRCPCH² |
Bee Wah Lee MD¹ | Hugo P. S. Van Bever PhD^{1,2}

¹Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

²Khoo Teck Puat-National University Children's Medical Institute, National University Hospital, National University Health System, Singapore, Singapore

Correspondence

Elizabeth Huiwen Tham, Division of Allergy & Immunology, Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, 1E Kent Ridge Road, Level 12 NUHS Tower Block, Singapore 119228, Singapore.
Email: elizabeth_tham@nuhs.edu.sg

Funding information

Tham EH is funded by the National Medical Research Council (NMRC) Research Training Fellowship Grant [MH 095:003\008-225] from the National Medical Research Council (NMRC), Singapore.

Editor: Hugh Sampson

Abstract

Atopic dermatitis (AD) is a chronic inflammatory skin disease mainly affecting children, which has no definitive curative therapy apart from natural outgrowing. AD is persistent in 30%-40% of children. Epithelial barrier dysfunction in AD is a significant risk factor for the development of epicutaneous food sensitization, food allergy, and other allergic disorders. There is evidence that prophylactic emollient applications from birth may be useful for primary prevention of AD, but biomarkers are needed to guide cost-effective targeted therapy for high-risk individuals. In established early-onset AD, secondary preventive strategies are needed to attenuate progression to other allergic disorders such as food allergy, asthma, and allergic rhinitis (the atopic march). This review aims to describe the mechanisms underpinning the development of epicutaneous sensitization to food allergens and progression to clinical food allergy; summarize current evidence for interventions to halt the progression from AD to food sensitization and clinical food allergy; and highlight unmet needs and directions for future research.

KEYWORDS

allergy prevention, anaphylaxis, atopic dermatitis, atopic march, epicutaneous sensitization, food allergens, food allergy, food hypersensitivity, nutrition, oral tolerance

1 | INTRODUCTION

Epithelial barrier dysfunction is a hallmark of atopic dermatitis (AD) and is attributable to a combination of structural, genetic, and environmental factors. Evidence suggests that early epithelial barrier dysfunction precedes the onset of AD and related allergic disorders. Kelleher et al found that increased transepidermal water loss (TEWL), a surrogate marker for skin barrier integrity, in the first week of life was associated with an increased risk of developing AD at 12 months of age.¹ There is also a strong causal relationship between AD and food allergy as a large proportion of infants with moderate-to-severe AD are also food-sensitized or food-allergic.²⁻⁴ Infants with early-onset AD are at increased risk of developing other allergic diseases such as asthma and allergic rhinitis in later childhood, in what has been termed the "atopic march."^{5,6} Data from clinical studies also suggest that food sensitization

and/or food allergies in early life are risk factors for the development of new allergen sensitization and allergic airway disorders.^{7,8}

This review aims to describe the mechanisms underpinning the development of epicutaneous sensitization to food allergens and its progression to clinical food allergy, summarize current evidence for interventions to halt the progression from AD to sensitization and food allergy, and discuss unmet needs and future research directions.

2 | SKIN BARRIER DYSFUNCTION IN AD

The skin is an important physical and immunologic barrier against the external environment, allergens, and microbes. Differentiating keratinocytes in the stratum basale (basal layer) progressively migrate upwards to reach the stratum corneum where they become

terminally differentiated and form corneocytes. The stratum corneum is made up of a cornified protein envelope containing corneocytes and keratin filaments which are cross-linked by filaggrin (FLG) and other structural proteins such as loricrin (LOR) and involucrin (IVL). Keratinocytes produce epidermal lipids, such as ceramides, which fill the spaces between corneocytes to form an impermeable hydrophobic skin barrier.⁹ Skin barrier integrity can be compromised by mutations in the FLG gene¹⁰ or other skin barrier proteins such as SPINK5¹¹ and corneodesmosin¹² which result in reduced expression of these and other structural skin barrier proteins including IVL and LOR; as well as deficiency of antimicrobial peptides (AMPs), altered epidermal lipid production, skin microbiome dysbiosis, and immune dysregulation.¹³ External factors such as repetitive scratching, reduced environmental humidity, allergens, bacteria such as *Staphylococcus aureus*, and topical irritants also inflict further mechanical damage to the skin barrier.

Th2 cytokines (IL-4/IL-13), which are predominant in AD, suppress the expression of epidermal proteins and ceramides, decrease antimicrobial peptide production by keratinocytes, and inhibit keratinocyte differentiation.^{14,15} Studies in different ethnic populations also support the role of other cytokines such as Th17 and Th22 responses in Asian and African populations, respectively.^{16,17}

The skin microbiome also plays an important role in AD pathogenesis and modulates disease trajectory. Up to 90% of AD patients are colonized with *Staphylococcus aureus* (*S aureus*). Pathogenic *S aureus* strains are more prevalent in AD skin than normal controls and are responsible for perpetuating disease persistence and morbidity.^{18,19} The skin microbiome dysbiosis in AD exacerbates skin barrier dysfunction, enhancing epicutaneous allergen sensitization. These skin changes are evident even at non-lesional sites²⁰ and are able to distinguish AD with food allergy from AD non-food allergy endophenotypes.²¹

Staphylococcus aureus superantigens stimulate IgE-mediated cytokine pathways, propagating downstream inflammatory responses without the need for antigen-presenting cells.^{22,23} They also induce glucocorticoid resistance,²⁴ contributing to failure of first-line topical steroid therapy in colonized patients, who may then require escalation to more potent immunomodulators.²⁵ Other pathogenic properties of *S aureus* include elaboration of α -toxin,²⁶ a potent cytotoxin responsible for keratinocyte cell death, protein A,²⁷ lipoteichoic acid (LTA),²⁸ proteases,²⁹ and the formation of biofilms³⁰ which act in tandem to disrupt the epidermal skin barrier. Clonal expansion of a single *S aureus* strain was observed in severe AD disease flares, which induced epidermal thickening and inflammatory responses in a murine skin model, to a significantly greater extent than those induced by commensal *S epidermidis* or *S aureus* isolates from patients with lower AD severity.³¹

Staphylococcal-derived superantigens, such as staphylococcal enterotoxin B (SEB), also enhance Th2 inflammation in the skin in response to peanut allergens and drive the development of peanut allergy.³² Jones et al³³ also observed that colonization with *S aureus*, particularly methicillin-resistant *S aureus* (MRSA), was associated with a higher risk of food allergy.

Key Message

Epicutaneous sensitization to food allergens in atopic dermatitis arises through an impaired skin barrier, skin microbial dysbiosis and immune dysregulation. This article review mechanisms behind these pathways and progression to clinical food allergy; summarizes current evidence for interventions to halt the progression from AD to food sensitization and clinical food allergy and highlights unmet needs and directions for future research.

3 | MECHANISMS FOR DEVELOPMENT OF EPICUTANEOUS SENSITIZATION TO FOOD ALLERGENS

There is now a considerable body of evidence demonstrating the mechanisms behind the development of epicutaneous food sensitization and pathways leading to clinical food allergy (Figure 1). The dual-allergen exposure hypothesis postulates that epicutaneous food sensitization occurs through an impaired skin barrier such as in AD, allowing allergen penetrance and cytokine dysregulation, which culminates in clinical food allergy. Early oral exposure to food allergens, however, promotes immune tolerance, potentially preventing development of food allergy.³⁴ Oral tolerance occurs when antigen-presenting cells in the gut mucosa are exposed to food allergens and induce differentiation of naive T cells into $\alpha 4\beta 7$ + gut-homing T cells.³⁵ These Tregs in turn induce production of Foxp3+ Tregs and elaboration of cytokines such as IL-10 and TGF- β , which inhibit Th2-dependent allergic responses and mast cell degranulation as well as production of IgG4.³⁶ Clinical food allergy thus occurs in the setting of a loss of skin barrier integrity, alongside a failure to achieve oral tolerance.

Genetic aberrations in skin barrier genes, such as loss-of-function mutations in FLG and SPINK5, result in reduced production of structural skin barrier proteins which are essential for the formation of an intact skin barrier, and have been linked to increased risks of food sensitization and/or food allergy.^{11,37}

Clinical studies also support this observation. Increased TEWL in 2-day-old neonates in the Babies After Scope: Evaluating the Longitudinal Impact Using Neurological and Nutritional Endpoints (BASELINE) birth cohort was predictive of food allergy at 2 years.³⁸ The Melbourne Atopy Cohort Study reported that children with AD at 6 months had increased risks of developing new-onset food and inhalant sensitization at 1 and 2 years of age.³⁹ In the Australian HealthNuts cohort, infants with AD within 1st year of life were 6 times more likely to have egg allergy and 11 times more likely to have peanut allergy by 12 months, particularly those with early-onset AD (<3 months of age) and those who had required topical steroid therapy.⁴⁰ African children with AD were also found to have a high prevalence of concomitant egg sensitization (54%) and egg allergy (25%).⁴¹

High environmental food allergen exposures increase the risks of epicutaneous food sensitization, particularly in the setting of skin

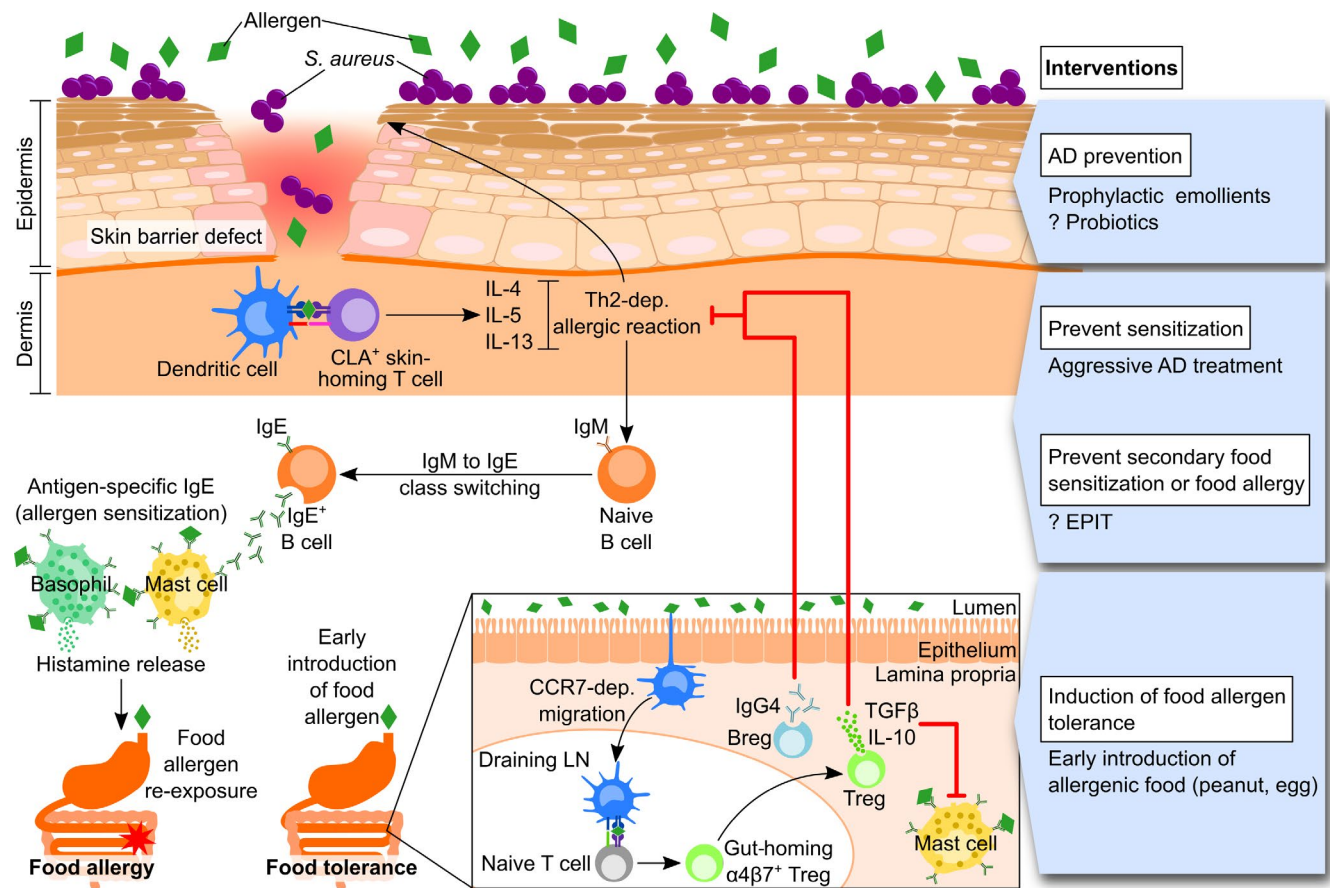


FIGURE 1 Epicutaneous sensitization in atopic dermatitis and intervention strategies. In atopic dermatitis (AD), an impaired skin barrier, skin microbiome dysbiosis, and cytokine dysregulation, along with subclinical environmental food allergen exposures, enhance risks of allergen sensitization and progression to clinical food allergy. Th2 cytokines also in turn suppress expression of skin barrier proteins which perpetuates the skin barrier defect. Intervention strategies under research currently target the various stages in the pathway: AD prevention, prevention of allergen sensitization, and prevention of secondary food sensitization/food allergy as well as induction of food allergy tolerance through early introduction of allergenic food (peanut and egg) in high-risk infants. The mechanism of oral tolerance occurs on exposure of antigen-presenting cells in the gut mucosa to food allergens, which induce differentiation of naive T cells into $\alpha 4 \beta 7^{+}$ gut-homing T cells. These Tregs in turn induce production of Foxp3⁺ Tregs and elaboration of cytokines such as IL-10 and TGF- β , which inhibit Th2-dependent allergic responses and mast cell degranulation as well as production of IgG4

barrier dysfunction. Adult occupational kitchen workers are exposed to frequent food handling. Kitchen workers with current hand eczema were found to have a 2-fold increased risk of current food allergy (adjusted odds ratio 2.4, 95% CI 1.6-3.7) compared to healthy controls.⁴² A greater severity of hand eczema also correlated with a higher likelihood of reported food-allergic symptoms and a diagnosis of food allergy.

In the Avon Longitudinal Study of Parents and Children, the application of peanut-containing skin preparations on inflamed skin was significantly associated with peanut allergy.⁴³ Brough et al⁴⁴ further described that environmental peanut protein levels in household dust were associated with increased odds of peanut sensitization and peanut allergy. These risks were augmented in children with AD, particularly those with increased AD severity and those with FLG mutations.^{44,45}

New-onset IgE-mediated wheat protein allergy and wheat-dependent exercise-induced anaphylaxis (WDEIA) cases were reported in previously healthy Japanese adults after topical exposure

to hydrolyzed wheat protein-containing facial soap on intact facial skin, which were attributed to epicutaneous sensitization to a high molecular weight glutenin allergenic epitope.^{46,47} These findings suggest that skin exposures to high concentrations of environmental food allergens increase the risks of epicutaneous sensitization, mainly in damaged skin.

4 | MECHANISTIC STUDIES

Evidence from mechanistic studies also demonstrates the immunologic pathways involved in the progression from epicutaneous sensitization to food allergy. A murine model of epicutaneous sensitization demonstrated that the application of food allergens on tape-stripped skin induced microscopic skin damage and inflammation akin to the skin barrier disruption seen in AD.⁴⁸ This was followed by recruitment of activated dendritic cells to the draining lymph nodes and expansion of allergen-specific IgG1 humoral responses

in the B-cell compartment of germinal centers in the early stages of epicutaneous food sensitization, generating a memory population of IgG1+ B cells. Repeated subclinical allergen exposure resulted in the generation of IgE+ germinal center B cells and serum IgE, demonstrating the progression from epicutaneous sensitization to IgE-mediated food sensitization and food allergy.

Chan et al³⁵ found a trend toward Th2 skewing in skin-homing CLA+ cells of peanut-allergic subjects, suggesting that allergic sensitization occurs through the skin, whereas Th1 skewing in gastrointestinal (GI)-homing $\alpha 4\beta 7$ + cells of peanut-tolerant subjects suggested that allergen exposure through the GI tract promotes tolerance (Figure 1). Strid et al observed that epicutaneous exposure to peanut protein in mice induced strong systemic Th2-type responses with high levels of IL-4 and serum IgE, which prevented the subsequent

induction of oral tolerance to peanut in an antigen-specific manner.⁴⁹ Upon oral peanut challenge, mice became further sensitized and developed strong peanut-specific IL-4 and IgE responses. Mice which were initially peanut-tolerant also became partly sensitized following epicutaneous peanut exposure. In another study, epicutaneous sensitization of mice via topical applications of OVA on tape-stripped skin resulted in IgE-dependent intestinal mast cell expansion, increased serum IL-4 levels, and systemic anaphylaxis following oral OVA challenge.⁵⁰ Noti et al⁵¹ found that OVA/peanut epicutaneously sensitized mice demonstrated TSLP-dependent basophil expansion in the skin, antigen-specific Th2 cytokine responses, increased antigen-specific serum IgE levels, and accumulation of mast cells in the intestine akin to IgE-mediated food allergy. Disruption of the TSLP-basophil axis was able to inhibit this allergic

TABLE 1 Strategies for prevention of AD, food sensitization, and food allergy

Strategy	Outcome	References
Prevention of AD		
Topical emollients from birth	Prevention of AD	Simpson, ⁵⁶ Horimukai ⁵⁷
Topical emollients (trilipid-rich ceramide-dominant) from birth	Prevention of AD	Lowe ⁵⁹
Probiotic supplementation in pregnancy or infancy	Weak evidence for prevention of AD	Doege, ⁶³ Wickens, ⁶⁴ Cuello-Garcia, ⁶⁵ Fiocchi ⁶⁶
Prebiotics	Insufficient evidence for AD prevention	Greer ⁶⁷
Hydrolyzed formulas		
Vitamin D supplementation		
Timing of solid food introduction	Insufficient evidence for AD prevention	Waidyatillake ⁶⁸
Prevention of food sensitization		
Aggressive AD treatment (PACI trial)	Prevention of food sensitization	Ohya ⁶⁹
Environmental food allergen avoidance	No studies	No studies
Breastfeeding alongside gluten introduction	Does not prevent wheat sensitization and allergy	Chmielewska ⁷⁷
Early egg introduction	Reduction in egg sensitization	Tan ⁹⁸
Prevention of food allergies		
Food allergen avoidance in pregnancy	Does not prevent food allergies	Kramer ⁸¹
Food allergen avoidance or delayed introduction in infancy	Does not prevent food allergies	Snijders, ⁸² Poole, ⁸³ Katz, ⁸⁴ Du toit, ⁸⁵ Koplin, ⁸⁶ Zeiger, ⁸⁷ Kajosaari, ⁸⁸ Zutavern ⁸⁹
Early peanut introduction in high-risk infants (LEAP and LEAP-On)	Prevention of peanut allergy	Du toit ⁹² Du toit ⁹³
Early introduction of heated egg in a 2-step regimen	Prevention of egg allergy	Natsume ¹⁰⁰
Timing of solid food introduction	Insufficient evidence for food allergy prevention	Obbagy ¹⁰⁷
Dietary diversity	Insufficient evidence for food allergy prevention	Obbagy ¹⁰⁷
Dietary patterns	Insufficient evidence for food allergy prevention	Obbagy ¹⁰⁷
Prevention of secondary food sensitization or food allergy		
Epicutaneous immunotherapy (EPIT) in OVA-sensitized mice	Protective effect against OVA-induced anaphylaxis	Tordesillas ¹¹⁰
Milk-specific EPIT in milk-sensitized mice	Prevention of peanut and HDM sensitization	Mondoulet ¹¹¹

response. Infiltration of IL-4-competent basophils and eosinophils was observed in the skin of these mice, indicating the central role of TSLP-dependent basophils in mediating Th2 responses in the pathogenesis of epicutaneously induced intestinal food allergy.⁵²

Galand et al⁵³ showed that mechanical skin damage induced by tape stripping induced local and systemic IL-33 release in OVA-sensitized mice, enhancing IgE-mediated mast cell degranulation and induced anaphylaxis upon oral antigen challenge. Conversely, disruption of IL-33 signaling through blockade of ST2 (the IL-33 receptor) inhibited these anaphylactic responses.

5 | INTERVENTIONAL STRATEGIES

Established AD has no definitive cure, apart from natural outgrowing in a proportion of children. Several birth cohort studies have indicated that between 30% and 40% of children with early-onset AD have persistent disease at 7-10 years of age.^{54,55} Current interventional strategies target the various stages in the epicutaneous sensitization-food allergy axis, in order to arrest progression through the atopic march. (Table 1 and Figure 1).

5.1 | Primary prevention of AD

Simpson et al⁵⁶ demonstrated that regular application of emollients from birth reduced the incidence of AD in high-risk 6-month-old infants (with a family history of AD) in the United States. At the same time, Horimukai et al⁵⁷ also reported reduced AD risk in 8-month-old high-risk Japanese infants who had been given prophylactic emollients from birth. In the latter study, children in the treatment group had a lower skin pH and increased proportions of commensal organisms at various skin sites compared to the control group, suggesting that these mechanisms may contribute to the preventive effects of emollients in high-risk infants.⁵⁸ The Prevention of AD By a Barrier Lipid Equilibrium Strategy (PEBBLES) study is an ongoing randomized controlled trial of 760 high-risk infants in whom topical applications of a trilipid-rich ceramide-dominant emollient were commenced from birth up to 6 months of age. Preliminary findings from this cohort showed decreased food sensitization at age 6 and 12 months in the treatment group compared to controls.⁵⁹ Further follow-up of these infants is ongoing to evaluate the efficacy of this intervention against challenge-proven food allergy by age 12 months, as well as skin barrier function, AD severity, and new-onset AD after treatment cessation.⁶⁰ Several other large ongoing trials aim to assess the efficacy of regular moisturizing for skin barrier protection in early life against the development of not just AD, but also challenge-proven food allergy and allergic airway diseases.^{61,62}

Consensus statements agree that there may be some evidence that probiotic supplementation in pregnancy or infancy is protective against the development of AD, but no protection against food allergy or other allergic disorders has yet been proven.⁶³⁻⁶⁶ There is also insufficient evidence for the use of other nutritive interventions such as prebiotics, hydrolyzed formulas, or vitamin D supplementation in

the primary prevention of allergic diseases.⁶⁷ A recent systematic review also concluded that there is currently insufficient evidence to provide recommendations on timing of solid food (allergenic and non-allergenic) introduction for AD prevention.⁶⁸

5.2 | Secondary prevention

5.2.1 | Preventing food sensitization

Secondary prevention involves interventions targeted at high-risk infants or children with AD, or food sensitization without clinical food allergy, aiming to prevent progression to clinical food allergy.

In established AD, early aggressive treatment aimed at reducing skin inflammation and repairing the defective skin barrier, thereby reducing the risks of developing food sensitization and food allergy. Individualized, stepwise treatment regimens are essential for children with AD, which comprise combinations of topical moisturizers for skin hydration and prevention of flares, topical anti-inflammatory medications, allergen avoidance, and early effective treatment of skin infections. The Japanese Prevention of Allergy via Cutaneous Intervention (PACI) study is an ongoing randomized controlled trial that plans to measure the effects of aggressive (proactive) treatment of 7- to 13-week-old infants with AD versus standard (reactive) AD treatment for the prevention of challenge-proven IgE-mediated hen's egg allergy at 28 weeks of age.⁶⁹

Reduction of environmental food allergen exposures may theoretically reduce risks of epicutaneous sensitization. However, subclinical environmental food allergen exposures are thought to be unable to induce overt allergic reactions but are able to induce food sensitization.^{48,70,71} Peanut protein spreads easily around a peanut-consuming home⁷² and is resistant to usual cleaning methods and may only be removed by the use of multiple different cleaning agents.⁷³ Peanut protein can also be transferred into the environment by means of hand transfer and saliva but is less likely to be aerosolized into vapor form to induce allergic reactions through inhalation.^{72,73} However, case reports of allergic reactions to airborne food particles have been reported.^{74,75}

In peanut-allergic children, household peanut consumption was positively correlated with peanut protein levels in the infant's bed-sheet and play area.⁷⁶ Household dust samples containing high peanut protein levels induced dose-dependent activation of basophils in children with peanut allergy, suggesting that environmental peanut protein exposures are linked to induction of food sensitization and food allergy. The efficacy of food allergen environmental avoidance measures for prevention of food sensitization, however, is currently doubtful. Restricting exposure to food allergens in the environment is practically impossible to achieve and difficult to study in formal randomized controlled trials. There are currently no studies available which investigate environmental food allergen avoidance for prevention of food sensitization.

A systematic review looking at early feeding practices and wheat sensitization/allergy found no evidence supporting the effectiveness of breastfeeding alongside gluten introduction against wheat

sensitization or wheat allergy.⁷⁷ Early introduction of gluten might reduce the risk of wheat sensitization, but there is currently no evidence that it reduces the risk of wheat allergy.

5.2.2 | Preventing progression to clinical food allergy

Early proponents of environmental allergen avoidance suggested that food allergen avoidance in pregnancy or early life could prevent development of food allergies.⁷⁸ The American Academy of Pediatrics (AAP) also recommended avoidance of cow's milk, egg, fish, peanuts, and tree nuts during lactation and that solid foods should not be introduced into the diet of high-risk infants until 6 months of age, with dairy products delayed until 1 year; eggs until 2 years; and peanuts, nuts, and fish until 3 years of age.⁷⁹ However, the prevalence of food allergies continued to rise over the ensuing two decades despite these measures.⁸⁰

Newer studies have since debunked this hypothesis. A systematic review by Kramer & Kakuma found that "prescription of an antigen avoidance diet to a high-risk woman during pregnancy was unlikely to reduce substantially her child's risk of atopic diseases, and such a diet may adversely affect maternal or fetal nutrition, or both."⁸¹ Katz et al⁸² observed that the delayed introduction of cow milk and other solid foods was associated with a higher risk for eczema and other atopic diseases at age 2 years. Delayed introduction of cereal grains after 6 months of life was also associated with an increased risk of IgE-mediated wheat allergy.⁸³ Israeli infants exposed to cow's milk in the first 14 days of life were also less likely to become cow's milk allergic compared to those with first exposure after 14 days.⁸⁴ Du Toit et al⁸⁵ observed a 10-fold lower prevalence of peanut allergy in Israeli children who consumed peanuts from early life, compared to peanut-avoiding Jewish children living in the UK. The Australian HealthNuts cohort also showed that delayed introduction of egg into infants' diets after 12 months of age was associated with a threefold higher risk of egg allergy⁸⁶ and that early introduction of cooked egg between the age of 4 and 6 months reduced this risk.

In response to the lack of evidence that delaying introduction of solids and allergenic foods had any protective effects on the development of food allergies,⁸⁷⁻⁸⁹ both the AAP and the National Institute of Allergy and Infectious Diseases (NIAID) replaced outdated guidelines with new recommendations that solid foods should not be delayed beyond 4-6 months of age.^{90,91}

Several randomized controlled trials subsequently showed that early introduction of allergenic foods such as peanut or egg to high-risk infants with severe AD or pre-existing food sensitization might reduce the risk of developing peanut or egg allergies, respectively. Four- to eleven-month-old high-risk infants with severe AD and/or egg allergy and peanut skin prick test (SPT) responses of 1-4 mm were enrolled in the Learning Early About Peanut Allergy (LEAP) trial. Infants randomized to consume 6 g of peanut protein at least 3 times a week, or 2 g 3 times a week, had an 81.4% lower risk of developing challenge-proven peanut allergy by age 5 years, compared to those who completely avoided peanut.⁹² This effect was sustained

up to 72 months.⁹³ This was the first Level 1 evidence indicating that early, rather than delayed, introduction of food allergens (specifically peanut) into the diet of high-risk infants could reduce the risk of developing food allergies. Several international bodies in Europe, the United States, and Australia then released guidelines recommending the early introduction of peanut in high-risk populations for the prevention of peanut allergy.⁹⁴⁻⁹⁶

Several other trials on the early introduction of allergenic foods have also been published.⁹⁷ Earlier trials did not show convincing evidence that the early introduction of egg (pasteurized whole egg, egg white powder, or heated egg powder) or other allergenic foods, apart from peanut, was able to reduce the risk of food allergy in normal or high-risk infants. While Tan et al⁹⁸ observed a significant reduction in egg sensitization at 1 year of age in infants in the early egg introduction group, this did not translate to a reduced risk of symptomatic allergy. In the Enquiring About Tolerance (EAT) study, normal-risk, fully breastfed 3-month-old infants in the UK were randomized regularly to consume 6 allergenic foods (peanut, cooked egg, cow's milk, sesame, white fish, and wheat) or to continue exclusive breastfeeding to around 6 months of age before introducing allergenic foods. However, the intention-to-treat analysis found no significant protection of early allergenic food introduction against food allergy development.⁹⁹ The PETIT (Prevention of Egg allergy with Tiny amount InTake) study, which investigated the effects of early introduction of heated egg powder to high-risk Japanese infants with AD on the development of egg allergy,¹⁰⁰ found that infants who consumed 50 mg heated whole egg powder between 6 and 9 months of age, then 250 mg between 9 and 12 months of age in a 2-step regimen, had 30% lower risk of developing challenge-proven hen's egg allergy at 12 months of age compared to the placebo group. AD severity in the intervention group, however, was lower than in the control group suggesting some degree of bias in the study. More well-randomized trials are thus needed to confirm the utility of early heated egg introduction for egg allergy prevention in children with AD.

A recent systematic review and meta-analysis indicated that there was "moderate-certainty evidence that introduction of egg to the infant diet at age 4-6 months was associated with reduced egg allergy and introduction of peanut at age 4-10 months was associated with reduced peanut allergy compared with later introduction of these foods."⁹⁷ The strength of evidence for egg introduction was weighted mainly by the PETIT study. Interestingly, although early peanut consumption reduced the risk of peanut allergy in high-risk infants, this appears to be allergen-specific as no protective effects were found against other food allergies such as tree nuts and sesame, other allergic disorders, or sensitization to other food allergens and also did not hasten the resolution of AD or egg allergy.¹⁰¹

The epidemiology and patterns of food allergy and anaphylaxis differ between geographic regions—such as a lower prevalence of overall food allergy; a relative paucity of peanut allergy and predominance of egg and wheat allergy in Asia; and unusual allergens such as beef in Eastern Europe and local delicacies in China.¹⁰²⁻¹⁰⁵ Recommendations for early introduction of allergenic foods in high-risk infants likely need to be modified to suit different populations.¹⁰⁶

There is currently also little evidence to indicate whether other interventions, such as the age of commencement of complementary feeding in general, dietary diversity, or dietary patterns, are protective against food allergy.¹⁰⁷

5.2.3 | Preventing progression to the atopic march

Epicutaneous immunotherapy (EPIT) is a relatively new therapeutic strategy which involves the topical application of relatively high concentrations of allergenic proteins on the skin of food-allergic patients to achieve desensitization, and is proposed to be a safer alternative to oral immunotherapy, albeit with lower efficacy.^{108,109} Chronic high doses of skin allergen exposure appear to induce IgG4-type responses compared to lower doses which skew toward Th2 responses and allergic sensitization. This mechanism is postulated to be responsible for the tolerogenic effects of EPIT as opposed to increasing sensitization, which is seen in subclinical low levels of allergen exposure in the environment.

Novel secondary prevention strategies, currently at the pre-clinical stage in murine models only, have now also proposed that EPIT might be utilized as a novel treatment strategy in existing food allergy or food sensitization to attenuate risks of developing new food allergies and/or progression to other allergic disorders such as asthma and allergic rhinitis.

Mice were first sensitized to ovalbumin (OVA) orally or through the skin and then treated with EPIT using OVA-Viaskin patches or OVA-based oral immunotherapy.¹¹⁰ Mice were then orally challenged with OVA to induce anaphylaxis. EPIT induced sustained protection against OVA-induced anaphylaxis through the generation of gastrointestinal-homing LAP⁺ Foxp3⁺ Treg cells. In another study, milk-specific EPIT administered to milk-sensitized mice prevented secondary sensitization to peanut or house dust mites.¹¹¹ EPIT significantly modified humoral responses, reduced TH2 cytokine levels, decreased eosinophilic esophageal infiltration, and suppressed airway hyper-responsiveness, and these protective effects were sustained over 2 months. Moreover, the adoptive transfer of milk EPIT Treg cells completely prevented sensitization to peanut and peanut-induced anaphylaxis. Further work into the mechanisms through which EPIT induces tolerance showed that 2 weeks of EPIT in OVA-sensitized mice induced Foxp3⁺ Treg cells in skin-draining lymph nodes and spleen.¹¹² After 8 weeks of treatment, these mice showed significant protection against anaphylaxis following oral challenge. At present, this has only been shown in one preclinical study and needs to be replicated in other in vivo models. Further research will subsequently be needed to evaluate the efficacy of this approach in larger human studies.

6 | FUTURE DIRECTIONS FOR RESEARCH

6.1 | Microbiome manipulation

Manipulation of the skin microbiome to reduce dysbiosis or to restore the healthy microbiome may potentially alter AD disease

course and associated morbidity. Myles et al¹¹³ found that topical application of *Roseomonas mucosa*, a skin commensal, taken from the skin of healthy volunteers but not from patients with AD, was associated with enhanced barrier function, innate immunity activation, and control of *S aureus* in an AD mouse model. In a follow-up open-label phase I/II trial (the Beginning Assessment of Cutaneous Treatment Efficacy for *Roseomonas* in atopic dermatitis trial; BACTERiAD I/II), treatment with *R mucosa* from healthy volunteers was associated with significant decreases in measures of disease severity, topical steroid requirement, and *S aureus* burden in AD subjects.¹¹⁴

In a separate study, coagulase-negative *Staphylococcus* (CoNS) strains with antimicrobial activity, through the production of previously unknown antimicrobial peptides (AMPs), were more commonly found on the skin of healthy subjects compared to AD subjects.¹¹⁵ These AMPs were potent, strain-specific, highly potent, and selectively killed *S aureus* on the skin of AD subjects. Colonization with a low frequency of these strains correlated with colonization by pathogenic *S aureus*. These CoNS strains demonstrated anti-*S aureus* activity when applied to mice and porcine in vivo skin models. Reintroduction of antimicrobial CoNS strains to human AD subjects furthermore decreased colonization by *S aureus*.

Skin microbiome transplants are now reaching clinical trials in human subjects. They involve the transfer of healthy skin microbiota from healthy volunteers onto AD skin with the aim of restoring a healthy skin microbiome, in the hopes of attaining long-term AD control. There are now several ongoing randomized clinical trials investigating the safety and efficacy of such targeted skin microbiome transplants on *S aureus* colonization in AD subjects [ClinicalTrials.gov identifiers NCT03151148 and NCT03158012]. These studies indicate exciting new possibilities for skin microbiome manipulation as a non-invasive topically administered treatment modality for severe AD, which may eventually be a means toward secondary prevention of AD-related comorbidities such as food sensitization, food allergy, and other allergic disorders. However, further in vitro and in vivo studies are needed to evaluate the efficacy of skin microbiome transplantation for AD prevention, epicutaneous food sensitization, and food allergy.

The gut microbiome is another potential target for interventions against food allergy. Evidence suggests that perturbations in gut microbiota are associated with AD in the first year of life and are also linked to food sensitization, food allergy, as well as other allergic disorders.¹¹⁶⁻¹²⁰ The gut metabolome, specifically short-chain fatty acids (SCFAs) which are the major metabolic end products of anaerobic bacterial fermentation in the gut,¹²¹ may also play an important role in the AD-food allergy axis. Butyrate, an important SCFA, potentially regulates inflammatory responses by modulating cytokine production, kinase activity, and transcription factors in various immune cell populations. It has been shown to increase the production of anti-inflammatory lipid mediators,¹²² decreases proinflammatory cytokine expression via inhibition of NF- κ B activation and I κ B α degradation,¹²³ and exerts immunomodulatory effects on various immune cell populations such as dendritic cells, T cells, monocytes, and mast cells.¹²⁴⁻¹²⁷

Roduit et al demonstrated that children with the highest levels of butyrate and propionate (≥ 95 th percentile) in feces at 1 year of age had significantly less atopic sensitization and were less likely to have a reported diagnosis of food allergy.¹²⁸ Infants with eczema by 18 months also showed discordant microbiota development in the first 26 weeks of life, namely decreased composition of lactate-utilizing butyrate producers, namely *Eubacterium* and *Anaerostipes*, which manifested with increased stool lactate and decreased butyrate levels.¹²⁹

Dietary manipulation of the gut microbiome in AD for prevention of food sensitization and food allergy is a potentially impactful intervention to be explored in future studies. While there is currently little evidence for the role of pre- or probiotics in food allergy prevention,^{130,131} this may be due to strain- or dose-dependent limitations. Various types of infant diets, such as those consisting of high levels of fruits, vegetables, and home-prepared foods,¹³² were reported to be associated with reduced risks of food allergy. More studies are needed to evaluate the effects of these interventions on the gut microbiota composition and the gut metabolome, and whether these play a role in food allergy prevention.

7 | CONTROVERSIES AND UNMET NEEDS

The skin plays an essential role in the pathogenesis of food allergy by having the ability to induce epicutaneous sensitization and is an emerging therapeutic medium for induction of tolerance through EPIT in established food allergy. The skin may also be a novel target for preventive strategies against de novo food allergy and development of multiple food allergies.

However, despite the plethora of knowledge on the mechanisms behind epicutaneous sensitization and the pathogenesis of food allergy, there are still many unmet needs. While high environmental food allergen levels have been shown to be linked to higher risks of food sensitization, interventions to reduce epicutaneous sensitization through environmental allergen avoidance are difficult to achieve realistically. There are also no studies on the effects of airborne food allergens on epicutaneous sensitization, nor the efficacy of reducing such exposures against food allergy development.

Little is known about the threshold of subclinical allergen exposure required to induce epicutaneous sensitization, nor the degree of skin barrier impairment which would allow sensitization to occur, to guide preventive interventions. Many commercial skin products now incorporate food proteins into their formulations to cater to consumers desiring more natural or organic ingredients. In light of new evidence that high levels of topical skin exposure to certain allergenic proteins can induce epicutaneous sensitization even through an intact skin barrier,^{46,47} controversy remains over whether there is a need for recommendations to avoid such exposures and to provide guidance for healthcare providers.

While primary preventive measures against AD such as prophylactic emollient therapy from birth show promise, predictive

biomarkers are still needed to guide recommendations for cost-effective targeted therapy for high-risk individuals.

Microbiome manipulation is an exciting new field which is a potentially non-invasive measure for primary or secondary preventive measures against AD and food allergy development. However, current studies are only observational and mostly in vivo models; thus, larger randomized controlled trials in humans are needed before more definite recommendations can be made.

ACKNOWLEDGMENT

The authors would like to thank Alicia Wong for her assistance with the figure illustration.

CONFLICT OF INTEREST

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors do not have any conflicts of interests to declare.

ORCID

Elizabeth Huiwen Tham  <https://orcid.org/0000-0003-1037-6143>

Mohana Rajakulendran  <https://orcid.org/0000-0001-7315-6709>

REFERENCES

1. Kelleher M, Dunn-Galvin A, Hourihane JO, et al. Skin barrier dysfunction measured by transepidermal water loss at 2 days and 2 months predates and predicts atopic dermatitis at 1 year. *J Allergy Clin Immunol*. 2015;135(4):930-5.e1.
2. Rennick GJ, Moore E, Orchard DC. Skin prick testing to food allergens in breast-fed young infants with moderate to severe atopic dermatitis. *Australas J Dermatol*. 2006;47(1):41-45.
3. Tsakok T, Marrs T, Mohsin M, et al. Does atopic dermatitis cause food allergy? A systematic review. *J Allergy Clin Immunol*. 2016;137(4):1071-1078.
4. Johansson EK, Bergstrom A, Kull I, et al. IgE sensitization in relation to preschool eczema and filaggrin mutation. *J Allergy Clin Immunol*. 2017;140(6):1572-9.e5.
5. Johansson E, Hershey G. Contribution of an impaired epithelial barrier to the atopic march. *Ann Allergy Asthma Immunol*. 2018;120(2):118-119.
6. Hill DA, Spergel JM. The atopic march: critical evidence and clinical relevance. *Ann Allergy Asthma Immunol*. 2018;120(2):131-137.
7. Host A, Halken S, Jacobsen HP, Christensen AE, Herskind AM, Plesner K. Clinical course of cow's milk protein allergy/intolerance and atopic diseases in childhood. *Pediatr Allergy Immunol*. 2002;13(s15):23-28.
8. Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol*. 1999;103(6):1173-1179.
9. Berdyshev E, Goleva E, Bronova I, et al. Lipid abnormalities in atopic skin are driven by type 2 cytokines. *JCI Insight*. 2018;3(4):e98006.
10. Barker JN, Palmer CN, Zhao Y, et al. Null mutations in the filaggrin gene (FLG) determine major susceptibility to early-onset atopic dermatitis that persists into adulthood. *J Invest Dermatol*. 2007;127(3):564-567.

11. Ashley SE, Tan HT, Vuillermin P, et al. The skin barrier function gene SPINK5 is associated with challenge-proven IgE-mediated food allergy in infants. *Allergy*. 2017;72(9):1356-1364.
12. Marenholz I, Esparza-Gordillo J, Lee YA. The genetics of the skin barrier in eczema and other allergic disorders. *Curr Opin Allergy Clin Immunol*. 2015;15(5):426-434.
13. Kim BE, Leung D. Significance of skin barrier dysfunction in atopic dermatitis. *Allergy Asthma Immunol Res*. 2018;10(3):207-215.
14. Gavrilova T. Immune dysregulation in the pathogenesis of atopic dermatitis. *Dermatitis*. 2018;29(2):57-62.
15. Czarnecki T, Krueger JG, Guttman-Yassky E. Skin barrier and immune dysregulation in atopic dermatitis: an evolving story with important clinical implications. *J Allergy Clin Immunol Pract*. 2014;2(4):371-379; quiz 80-1.
16. Noda S, Suarez-Farinas M, Ungar B, et al. The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization. *J Allergy Clin Immunol*. 2015;136(5):1254-1264.
17. Sanyal RD, Pavel AB, Glickman J, et al. Atopic dermatitis in African American patients is TH2/TH22-skewed with TH1/TH17 attenuation. *Ann Allergy Asthma Immunol*. 2019;122(1):99-110.e6.
18. Totte JE, van der Feltz WT, Hennekam M, van Belkum A, van Zuuren EJ, Pasmans SG. Prevalence and odds of *Staphylococcus aureus* carriage in atopic dermatitis: a systematic review and meta-analysis. *Br J Dermatol*. 2016;175:687-695.
19. Spaulding AR, Salgado-Pabon W, Kohler PL, Horswill AR, Leung DY, Schlievert PM. Staphylococcal and streptococcal superantigen exotoxins. *Clin Microbiol Rev*. 2013;26(3):422-447.
20. Tauber M, Balica S, Hsu CY, et al. *Staphylococcus aureus* density on lesional and nonlesional skin is strongly associated with disease severity in atopic dermatitis. *J Allergy Clin Immunol*. 2016;137(4):1272-4.e3.
21. Leung D, Calatroni A, Zaramela LS, et al. The nonlesional skin surface distinguishes atopic dermatitis with food allergy as a unique endotype. *Sci Transl Med*. 2019;11(480):eaav2685.
22. Bunikowski R, Mielke M, Skarabis H, et al. Prevalence and role of serum IgE antibodies to the *Staphylococcus aureus*-derived superantigens SEA and SEB in children with atopic dermatitis. *J Allergy Clin Immunol*. 1999;103(1 Pt 1):119-124.
23. Leung DY, Harbeck R, Bina P, et al. Presence of IgE antibodies to staphylococcal exotoxins on the skin of patients with atopic dermatitis. Evidence for a new group of allergens. *J Clin Invest*. 1993;92(3):1374-1380.
24. Hauk PJ, Hamid QA, Chrousos GP, Leung DY. Induction of corticosteroid insensitivity in human PBMCs by microbial superantigens. *J Allergy Clin Immunol*. 2000;105(4):782-787.
25. Leung DY, Hanifin JM, Pariser DM, et al. Effects of pimecrolimus cream 1% in the treatment of patients with atopic dermatitis who demonstrate a clinical insensitivity to topical corticosteroids: a randomized, multicentre vehicle-controlled trial. *Br J Dermatol*. 2009;161(2):435-443.
26. Brauweiler AM, Goleva E, Leung D. Th2 cytokines increase *Staphylococcus aureus* alpha toxin-induced keratinocyte death through the signal transducer and activator of transcription 6 (STAT6). *J Invest Dermatol*. 2014;134(8):2114-2121.
27. Classen A, Kalali BN, Schnopp C, et al. TNF receptor I on human keratinocytes is a binding partner for staphylococcal protein A resulting in the activation of NF kappa B, AP-1, and downstream gene transcription. *Exp Dermatol*. 2011;20(1):48-52.
28. Brauweiler AM, Goleva E, Leung D. *Staphylococcus aureus* lipoteichoic acid damages the skin barrier through an IL-1 mediated pathway. *J Invest Dermatol*. 2019;139(8):1753-1761.e4.
29. Nakatsuji T, Chen TH, Two AM, et al. *Staphylococcus aureus* exploits epidermal barrier defects in atopic dermatitis to trigger cytokine expression. *J Invest Dermatol*. 2016;136(11):2192-2200.
30. Gonzalez T, Biagini Myers JM, Herr AB, Khurana Hershey GK. Staphylococcal biofilms in atopic dermatitis. *Curr Allergy Asthma Rep*. 2017;17(12):81.
31. Byrd AL, Deming C, Cassidy S, et al. *Staphylococcus aureus* and *Staphylococcus epidermidis* strain diversity underlying pediatric atopic dermatitis. *Sci Transl Med*. 2017;9(397):eaal4651.
32. Forbes-Blom E, Camberis M, Prout M, Tang SC, Le Gros G. Staphylococcal-derived superantigen enhances peanut induced Th2 responses in the skin. *Clin Exp Allergy*. 2012;42(2):305-314.
33. Jones AL, Curran-Everett D, Leung D. Food allergy is associated with *Staphylococcus aureus* colonization in children with atopic dermatitis. *J Allergy Clin Immunol*. 2016;137(4):1247-8.e3.
34. Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol*. 2008;121(6):1331-1336.
35. Chan SM, Turcanu V, Stephens AC, Fox AT, Grieve AP, Lack G. Cutaneous lymphocyte antigen and alpha4beta7 T-lymphocyte responses are associated with peanut allergy and tolerance in children. *Allergy*. 2012;67(3):336-342.
36. Weiner HL, da Cunha AP, Quintana F, Wu H. Oral tolerance. *Immunol Rev*. 2011;241(1):241-259.
37. Venkataraman D, Soto-Ramirez N, Kurukulaaratchy RJ, et al. Filaggrin loss-of-function mutations are associated with food allergy in childhood and adolescence. *J Allergy Clin Immunol*. 2014;134(4):876-82.e4.
38. Kelleher MM, Dunn-Galvin A, Gray C, et al. Skin barrier impairment at birth predicts food allergy at 2 years of age. *J Allergy Clin Immunol*. 2016;137(4):1111-6.e8.
39. Lowe AJ, Abramson MJ, Hosking CS, et al. The temporal sequence of allergic sensitization and onset of infantile eczema. *Clin Exp Allergy*. 2007;37(4):536-542.
40. Martin PE, Eckert JK, Koplin JJ, et al. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clin Exp Allergy*. 2015;45(1):255-264.
41. Gray CL, Levin ME, du Toit G. Egg sensitization, allergy and component patterns in African children with atopic dermatitis. *Pediatr Allergy Immunol*. 2016;27(7):709-715.
42. Minami T, Fukutomi Y, Sekiya K, Akasawa A, Taniguchi M. Hand eczema as a risk factor for food allergy among occupational kitchen workers. *Allergol Int*. 2018;67(2):217-224.
43. Lack G, Fox D, Northstone K, Golding J. Factors associated with the development of peanut allergy in childhood. *N Engl J Med*. 2003;348(11):977-985.
44. Brough HA, Liu AH, Sicherer S, et al. Atopic dermatitis increases the effect of exposure to peanut antigen in dust on peanut sensitization and likely peanut allergy. *J Allergy Clin Immunol*. 2015;135(1):164-170.
45. Brough HA, Simpson A, Makinson K, et al. Peanut allergy: effect of environmental peanut exposure in children with filaggrin loss-of-function mutations. *J Allergy Clin Immunol*. 2014;134(4):867-75.e1.
46. Fukutomi Y, Taniguchi M, Nakamura H, Akiyama K. Epidemiological link between wheat allergy and exposure to hydrolyzed wheat protein in facial soap. *Allergy*. 2014;69(10):1405-1411.
47. Yokooji T, Kurihara S, Murakami T, et al. Characterization of causative allergens for wheat-dependent exercise-induced anaphylaxis sensitized with hydrolyzed wheat proteins in facial soap. *Allergol Int*. 2013;62(4):435-445.
48. Jimenez-Saiz R, Ellenbogen Y, Koenig J, et al. IgG1(+) B-cell immunity predates IgE responses in epicutaneous sensitization to foods. *Allergy*. 2019;74(1):165-175.
49. Strid J, Hourihane J, Kimber I, Callard R, Strobel S. Epicutaneous exposure to peanut protein prevents oral tolerance and enhances allergic sensitization. *Clin Exp Allergy*. 2005;35(6):757-766.
50. Bartnikas LM, Gurish MF, Burton OT, et al. Epicutaneous sensitization results in IgE-dependent intestinal mast cell expansion and food-induced anaphylaxis. *J Allergy Clin Immunol*. 2013;131(2):451-460.e6.

51. Noti M, Kim BS, Siracusa MC, et al. Exposure to food allergens through inflamed skin promotes intestinal food allergy through the thymic stromal lymphopoietin-basophil axis. *J Allergy Clin Immunol*. 2014;133(5):1390-1399, 9, e1-6.
52. Hussain M, Borcard L, Walsh KP, et al. Basophil-derived IL-4 promotes epicutaneous antigen sensitization concomitant with the development of food allergy. *J Allergy Clin Immunol*. 2018;141(1):223-34.e5.
53. Galand C, Leyva-Castillo JM, Yoon J, et al. IL-33 promotes food anaphylaxis in epicutaneously sensitized mice by targeting mast cells. *J Allergy Clin Immunol*. 2016;138(5):1356-1366.
54. Hua TC, Hwang CY, Chen YJ, et al. The natural course of early-onset atopic dermatitis in Taiwan: a population-based cohort study. *Br J Dermatol*. 2014;170(1):130-135.
55. Carlsten C, Dimich-Ward H, Ferguson A, et al. Atopic dermatitis in a high-risk cohort: natural history, associated allergic outcomes, and risk factors. *Ann Allergy Asthma Immunol*. 2013;110(1):24-28.
56. Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol*. 2014;134(4):818-823.
57. Horimukai K, Morita K, Narita M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(4): 824-830.e6.
58. Glatz M, Jo JH, Kennedy EA, et al. Emollient use alters skin barrier and microbes in infants at risk for developing atopic dermatitis. *PLoS ONE*. 2018;13(2):e0192443.
59. Lowe AJ, Su JC, Allen KJ, et al. A randomized trial of a barrier lipid replacement strategy for the prevention of atopic dermatitis and allergic sensitization: the PEBBLES pilot study. *Br J Dermatol*. 2018;178(1):e19-e21.
60. Lowe A, Su J, Tang M, et al. PEBBLES study protocol: a randomised controlled trial to prevent atopic dermatitis, food allergy and sensitisation in infants with a family history of allergic disease using a skin barrier improvement strategy. *BMJ Open*. 2019;9(3):e024594.
61. Chalmers JR, Haines RH, Mitchell EJ, et al. Effectiveness and cost-effectiveness of daily all-over-body application of emollient during the first year of life for preventing atopic eczema in high-risk children (The BEEP trial): protocol for a randomised controlled trial. *Trials*. 2017;18(1):343.
62. Lowe AJ, Leung D, Tang M, Su JC, Allen KJ. The skin as a target for prevention of the atopic march. *Ann Allergy Asthma Immunol*. 2018;120(2):145-151.
63. Doege K, Grajecki D, Zyriax BC, Detinkina E, Zu Eulenburg C, Buhling KJ. Impact of maternal supplementation with probiotics during pregnancy on atopic eczema in childhood—a meta-analysis. *Br J Nutr*. 2012;107(1):1-6.
64. Wickens K, Black PN, Stanley TV, et al. A differential effect of 2 probiotics in the prevention of eczema and atopy: a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2008;122(4):788-794.
65. Cuello-Garcia CA, Brozek JL, Fiocchi A, et al. Probiotics for the prevention of allergy: a systematic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol*. 2015;136(4):952-961.
66. Fiocchi A, Pawankar R, Cuello-Garcia C, et al. World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): probiotics. *World Allergy Organ J*. 2015;8(1):4.
67. Greer FR, Sicherer SH, Burks AW. The effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, hydrolyzed formulas, and timing of introduction of allergenic complementary foods. *Pediatrics*. 2019;143(4):e20190281.
68. Waidyatillake NT, Dharmage SC, Allen KJ, et al. Association between the age of solid food introduction and eczema: a systematic review and a meta-analysis. *Clin Exp Allergy*. 2018;48(8):1000-1015.
69. Ohya Y. Early Aggressive Intervention for Infantile Atopic Dermatitis to Prevent Development of Food Allergy: a Multicenter, Investigator-Blinded, Randomized, Parallel Group Controlled Trial (PACI Study). UMIN-CTR Trial Registration ID: UMIN000028043. http://paci-study.jp/english.htmlhttps://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000031912. Accessed 1 May, 2019.
70. Greenhawt M. Environmental exposure to peanut and the risk of an allergic reaction. *Ann Allergy Asthma Immunol*. 2018;120(5):476-81.e3.
71. Simonte SJ, Ma S, Mofidi S, Sicherer SH. Relevance of casual contact with peanut butter in children with peanut allergy. *J Allergy Clin Immunol*. 2003;112(1):180-182.
72. Perry TT, Conover-Walker MK, Pomes A, Chapman MD, Wood RA. Distribution of peanut allergen in the environment. *J Allergy Clin Immunol*. 2004;113(5):973-976.
73. Brough HA, Makinson K, Penagos M, et al. Distribution of peanut protein in the home environment. *J Allergy Clin Immunol*. 2013;132(3):623-629.
74. Leonardi S, Pecoraro R, Filippelli M, et al. Allergic reactions to foods by inhalation in children. *Allergy Asthma Proc*. 2014;35(4):288-294.
75. Furlong TJ, DeSimone J, Sicherer SH. Peanut and tree nut allergic reactions in restaurants and other food establishments. *J Allergy Clin Immunol*. 2001;108(5):867-870.
76. Brough HA, Santos AF, Makinson K, et al. Peanut protein in household dust is related to household peanut consumption and is biologically active. *J Allergy Clin Immunol*. 2013;132(3):630-638.
77. Chmielewska A, Piescik-Lech M, Shamir R, Szajewska H. Systematic review: early infant feeding practices and the risk of wheat allergy. *J Paediatr Child Health*. 2017;53(9):889-896.
78. Arshad SH. Allergen avoidance and prevention of atopy. *Curr Opin Allergy Clin Immunol*. 2004;4(2):119-123.
79. American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics*. 2000;106(2 Pt 1):346-349.
80. Prescott S, Allen KJ. Food allergy: riding the second wave of the allergy epidemic. *Pediatr Allergy Immunol*. 2011;22(2):155-160.
81. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database Syst Rev*. 2012;9:CD000133.
82. Snijders BE, Thijs C, van Ree R, van den Brandt PA. Age at first introduction of cow milk products and other food products in relation to infant atopic manifestations in the first 2 years of life: the KOALA Birth Cohort Study. *Pediatrics*. 2008;122(1):e115-e122.
83. Poole JA, Barriga K, Leung DY, et al. Timing of initial exposure to cereal grains and the risk of wheat allergy. *Pediatrics*. 2006;117(6):2175-2182.
84. Katz Y, Rajuan N, Goldberg MR, et al. exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. *J Allergy Clin Immunol*. 2010;126(1):77-82.e1.
85. Du Toit G, Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol*. 2008;122(5):984-991.
86. Koplin JJ, Osborne NJ, Wake M, et al. Can early introduction of egg prevent egg allergy in infants? A population-based study. *J Allergy Clin Immunol*. 2010;126(4):807-813.
87. Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol*. 1995;95(6):1179-1190.
88. Kajosaari M. Atopy prophylaxis in high-risk infants. Prospective 5-year follow-up study of children with six months exclusive breastfeeding and solid food elimination. *Adv Exp Med Biol*. 1991;310:453-458.
89. Zutavern A, Brockow I, Schaaf B, et al. Timing of solid food introduction in relation to atopic dermatitis and atopic

- sensitization: results from a prospective birth cohort study. *Pediatrics*. 2006;117(2):401-411.
90. Greer FR, Sicherer SH, Burks AW, American Academy of Pediatrics Committee on Nutrition, American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics*. 2008;121(1):183-191.
 91. Boyce JA, Assa'a A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-Sponsored Expert Panel Report. *Nutrition*. 2011;27(2):253-267.
 92. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372(9):803-813.
 93. Du Toit G, Sayre PH, Roberts G, et al. Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med*. 2016;374(15):1435-1443.
 94. Fleischer DM, Sicherer S, Greenhawt M, et al. Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. *J Allergy Clin Immunol*. 2015;136(2):258-261.
 95. Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. *J Allergy Clin Immunol*. 2017;139(1):29-44.
 96. Joshi PA, Smith J, Vale S, Campbell DE. The Australasian Society of Clinical Immunology and Allergy infant feeding for allergy prevention guidelines. *Med J Aust*. 2019;210(2):89-93.
 97. Ierodiakonou D, Garcia-Larsen V, Logan A, et al. Timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease: a systematic review and meta-analysis. *JAMA*. 2016;316(11):1181-1192.
 98. Wei-Liang Tan J, Valerio C, Barnes EH, et al. A randomized trial of egg introduction from 4 months of age in infants at risk for egg allergy. *J Allergy Clin Immunol*. 2017;139(5):1621-1628 e8.
 99. Perkin MR, Logan K, Tseng A, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med*. 2016;374(18):1733-1743.
 100. Natsume O, Kabashima S, Nakazato J, et al. Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema (PETIT): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;389(10066):276-286.
 101. du Toit G, Sayre PH, Roberts G, et al. Allergen specificity of early peanut consumption and effect on development of allergic disease in the Learning Early About Peanut Allergy study cohort. *J Allergy Clin Immunol*. 2018;141(4):1343-1353.
 102. Tham EH, Lee BW, Chan YH, et al. Food allergy prevalence despite delayed introduction of allergenic foods-data from the GUSTO cohort. *J Allergy Clin Immunol Pract*. 2017;6:466-475.e1.
 103. Tham EH, Leung A, Pacharn P, et al. Anaphylaxis – lessons learnt when East meets West. *Pediatr Allergy Immunol*. 2019. <https://doi.org/10.1111/pai.13098>
 104. Fedorova OS, Ogorodova LM, Fedotova MM, Evdokimova TA. The prevalence of food allergy to peanut and hazelnut in children in Tomsk Region. *Vopr Pitan*. 2014;83(1):48-54.
 105. Orhan F, Karakas T, Cakir M, Aksoy A, Baki A, Gedik Y. Prevalence of immunoglobulin E-mediated food allergy in 6-9-year-old urban schoolchildren in the eastern Black Sea region of Turkey. *Clin Exp Allergy*. 2009;39(7):1027-1035.
 106. Tham EH, Shek LP, Van Bever HP, et al. Early introduction of allergenic foods for the prevention of food allergy from an Asian perspective-An Asia Pacific Association of Pediatric Allergy, Respiriology & Immunology (APAPARI) consensus statement. *Pediatr Allergy Immunol*. 2018;29(1):18-27.
 107. Obbagy JE, English LK, Wong YP, et al. Complementary feeding and food allergy, atopic dermatitis/eczema, asthma, and allergic rhinitis: a systematic review. *Am J Clin Nutr*. 2019;109(Suppl 7):890s-934s.
 108. Lanser BJ, Leung D. The current state of epicutaneous immunotherapy for food allergy: a comprehensive review. *Clin Rev Allergy Immunol*. 2018;55(2):153-161.
 109. Jones SM, Sicherer SH, Burks AW, et al. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. *J Allergy Clin Immunol*. 2017;139(4):1242-52.e9.
 110. Tordesillas L, Mondoulet L, Blazquez AB, Benhamou PH, Sampson HA, Berin MC. Epicutaneous immunotherapy induces gastrointestinal LAP(+) regulatory T cells and prevents food-induced anaphylaxis. *J Allergy Clin Immunol*. 2017;139(1):189-201.e4.
 111. Mondoulet L, Dioszeghy V, Puteaux E, et al. Specific epicutaneous immunotherapy prevents sensitization to new allergens in a murine model. *J Allergy Clin Immunol*. 2015;135(6):1546-57.e4.
 112. Dioszeghy V, Mondoulet L, Laoubi L, et al. Antigen uptake by langerhans cells is required for the induction of regulatory T cells and the acquisition of tolerance during epicutaneous immunotherapy in OVA-sensitized mice. *Front Immunol*. 2018;9:1951.
 113. Myles IA, Williams KW, Reckhow JD, et al. Transplantation of human skin microbiota in models of atopic dermatitis. *JCI Insight*. 2016;1(10).
 114. Myles IA, Earland NJ, Anderson ED, et al. First-in-human topical microbiome transplantation with *Roseomonas mucosa* for atopic dermatitis. *JCI Insight*. 2018;3(9).
 115. Nakatsuji T, Chen TH, Narala S, et al. Antimicrobials from human skin commensal bacteria protect against *Staphylococcus aureus* and are deficient in atopic dermatitis. *Sci Transl Med*. 2017;9(378):eaah4680.
 116. Abrahamsson TR, Jakobsson HE, Andersson AF, Bjorksten B, Engstrand L, Jenmalm MC. Low diversity of the gut microbiota in infants with atopic eczema. *J Allergy Clin Immunol*. 2012;129(2):434-440, 40.e1-2.
 117. Chen CC, Chen KJ, Kong MS, Chang HJ, Huang JL. Alterations in the gut microbiotas of children with food sensitization in early life. *Pediatr Allergy Immunol*. 2016;27(3):254-262.
 118. Ling Z, Li Z, Liu X, et al. Altered fecal microbiota composition associated with food allergy in infants. *Appl Environ Microbiol*. 2014;80(8):2546-2554.
 119. Dzidic M, Abrahamsson TR, Artacho A, et al. Aberrant IgA responses to the gut microbiota during infancy precede asthma and allergy development. *J Allergy Clin Immunol*. 2017;139(3):1017-25.e14.
 120. Azad MB, Konya T, Guttman DS, et al. Infant gut microbiota and food sensitization: associations in the first year of life. *Clin Exp Allergy*. 2015;45(3):632-643.
 121. Cummings JH. Short chain fatty acids in the human colon. *Gut*. 1981;22(9):763-779.
 122. Kovarik JJ, Holzl MA, Hofer J, et al. Eicosanoid modulation by the short-chain fatty acid n-butyrate in human monocytes. *Immunology*. 2013;139(3):395-405.
 123. Segain JP, Raingeard de la Bletiere D, Bourreille A, et al. Butyrate inhibits inflammatory responses through NF- κ B inhibition: implications for Crohn's disease. *Gut*. 2000;47(3):397-403.
 124. Liu L, Li L, Min J, et al. Butyrate interferes with the differentiation and function of human monocyte-derived dendritic cells. *Cell Immunol*. 2012;277(1-2):66-73.
 125. Diakos C, Prieschl EE, Saemann MD, et al. n-Butyrate inhibits Jun NH(2)-terminal kinase activation and cytokine transcription in mast cells. *Biochem Biophys Res Commun*. 2006;349(2):863-868.
 126. Millard AL, Mertes PM, Ittelet D, Villard F, Jeannesson P, Bernard J. Butyrate affects differentiation, maturation and function of human monocyte-derived dendritic cells and macrophages. *Clin Exp Immunol*. 2002;130(2):245-255.

127. Arpaia N, Campbell C, Fan X, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature*. 2013;504(7480):451-455.
128. Roduit C, Frei R, Ferstl R, et al. High levels of butyrate and propionate in early life are associated with protection against atopy. *Allergy*. 2019;74(4):799-809.
129. Wopereis H, Sim K, Shaw A, Warner JO, Knol J, Kroll JS. Intestinal microbiota in infants at high risk for allergy: effects of prebiotics and role in eczema development. *J Allergy Clin Immunol*. 2018;141(4):1334-42.e5.
130. Zhang GQ, Hu HJ, Liu CY, Zhang Q, Shakya S, Li ZY. Probiotics for prevention of atopy and food hypersensitivity in early childhood: a PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. *Medicine*. 2016;95(8):e2562.
131. Muraro A, Halken S, Arshad SH, et al. EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. *Allergy*. 2014;69(5):590-601.
132. Grimshaw KE, Maskell J, Oliver EM, et al. Diet and food allergy development during infancy: birth cohort study findings using prospective food diary data. *J Allergy Clin Immunol*. 2014;133(2):511-519.

How to cite this article: Tham EH, Rajakulendran M, Wah LB, Van Bever HPS. Epicutaneous sensitization to food allergens in atopic dermatitis: What do we know? *Pediatr Allergy Immunol*. 2020;31:7-18. <https://doi.org/10.1111/pai.13127>