Early intervention and prevention of allergic diseases

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Abstract

Food Allergy (FA) is now one of the most common chronic diseases of childhood often lasting throughout life and leading to significant worldwide healthcare burden. The precise mechanisms responsible for the development of this inflammatory condition are largely unknown; however, a multifactorial aetiology involving both environmental and genetic contributions is well accepted. A precise understanding of the pathogenesis of FA is an essential first step to developing comprehensive prevention strategies that could mitigate this epidemic. As it is frequently preceded by atopic dermatitis and can be prevented by early antigen introduction, the development of FA is likely facilitated by the improper initial presentation of antigen to the developing immune system. Primary oral exposure of antigens allowing for presentation via a well-developed mucosal immune system, rather than through a disrupted skin epidermal barrier, is essential to prevent FA. In this review, we present the data supporting the necessity of 1) an intact epidermal barrier to prevent epicutaneous antigen presentation, 2) the presence of specific commensal bacteria to maintain an intact mucosal immune system and 3) maternal/infant diet diversity, including vitamins and minerals, and appropriately timed allergenic food introduction to prevent FA.

Introduction:

Atopic conditions, including atopic dermatitis (AD), food and environmental allergies and asthma, have become an important public health concern world-wide.[1] This review will focus primarily on early interventions to prevent food allergy (FA).[2-4] Recent studies reinforce the strong connection between early severe AD and the development of FA. Pediatric FA has become an epidemic in many countries, with increasing rates in the past few decades, although substantial variations from 1% to 10% exist by country. To date, some of the highest rates have been observed in high-income countries such as the United Kingdom, United States, and Australia, where population-based surveys and analyses of healthcare utilization data suggest the burden of disease has substantially increased.[5-9] While there is consensus that prevalence has increased

in many parts of the world, the magnitude is difficult to ascertain due to numerous factors, including a lack of systematic population-based surveillance efforts incorporating repeated, validated prevalence assessments, and high-quality estimates lacking from many countries. Figure 1 visualizes the most recently available population-based estimates of pediatric FA prevalence.[10-12]

It is also difficult to estimate FA prevalence globally or compare rates by country because of the limited international coordination of disease surveillance efforts, leading to heterogeneity in study design, FA case definitions, and study populations.[10,13]Even in studies with similar populations, direct comparisons of prevalence rates are challenging as there are variations in social, cultural, and economic factors. Despite the literature gaps, extensive research into paediatric FA epidemiology provides insight into possible FA aetiology and promising disease prevention avenues. For example, an epidemiologic finding of disparate rates of infant peanut allergy among genetically similar populations in the UK and Israel led to insights regarding the protective role of early life exposure to major food allergens.[14] These insights have now been tested in randomized controlled trials (RCTs) and translated into clinical practice guidelines that advocate the early introduction of allergenic solids for primary prevention.[15-17]

The multifactorial aetiology of FA is well-recognised, with environmental and genetic factors contributing to FA development. However, strategies to manage FA remain limited in most cases to strict allergen avoidance and managing allergic reactions, including teaching patients/caregivers to administer epinephrine during suspected anaphylaxis, which can adversely impact patient/caregiver quality of life. [18] Food allergen immunotherapy appears to offer transient protection but is allergen-specific, time-intensive, and side effects limit tolerability.[19] Even when gold standard treatments exist, prevention remains the ultimate goal since it can circumvent early morbidity from disease and ameliorate treatment burden.

AD often heralds the atopic march and frequently precedes the development of FA, allergic asthma and allergic rhinitis. Whether AD is the primary insult, or the earliest manifestation of other underlying factors is not yet fully established. However, AD is a significant risk factor for FA and may play a key role in FA prevention. Numerous studies suggest a causal role of cutaneous sensitization in FA's development where both the skin barrier and immunology are thought to be key players.[20]

The true global prevalence for AD is also unclear, with previous studies indicating paediatric AD prevalence varying by country.[21] Between 1999-2004 the International Study of Asthma and Allergies in Childhood incorporated a standardized school-based sampling methodology and symptom questionnaire to estimate current AD prevalence among 6-7-year-olds in 60 countries and estimates for 13-14-year-olds in 96 countries. Subsequent studies have independently verified the increase of increasing several countries. These landmark findings are visualized in Figures 2 and 3. However, they are nearly 20 years old, and no comparable effort to systematically assess longitudinal changes in the global prevalence of AD has since been undertaken.

The dietary impact of early life nutrition is another staple of FA prevention. It has been studied to varying degrees, including the impact of oral tolerance induction, breast and formula feeding, Vitamin D, dietary diversity, and the role of pre-, pro-and syn-biotics. The interaction of the skin and diet come together in the interplay between oral tolerance induction and epicutaneous allergen exposure. This forms the basis of the dual-allergen exposure hypothesis, which proposes that epicutaneous food allergen exposure in early life is associated with the development of FA, whilst early life oral exposure is protective.[22-24]

Finally, microbial factors may impact FA prevention with the mode of delivery at birth, pet exposure and bacterial (*S. aureus*) colonisation. The roles of viruses and fungi are still unknown. This review will explore AD, the infant diet, microbial factors, and the complex interplay of all factors in FA development, focusing primarily on early intervention to prevent FA. We conclude our review with a discussion of future and ongoing research including key topics that must be addressed.

Cutaneous factors and environmental exposures in the development of FA

Early AD is implicated in the subsequent development of allergic diseases, including FA, asthma, allergic rhinitis and is termed the "atopic march".[2-4] In the "outside-in" hypothesis, skin barrier defect allows

penetration of allergens and microbes leading to atopic sensitization whereas, in the "inside-out" paradigm, a polarized immune response leads to a defective skin barrier (Figure 4).[25]

Experimental models and clinical observations in humans support the concept of epicutaneous food allergen sensitization.[20,26]The epidermis plays a key role in preventing allergens, irritants and microbes from penetrating the skin and eliciting the host immune response. These events are facilitated by skin barrier dysfunction in AD, promoting the penetration of food allergens from topical application or the environment. Lack et al.[23] first reported that peanut allergy was associated with the topical application of skin creams containing peanut protein. Subsequently, Fox et al.[24] reported increased FA in households that ate peanuts. In addition, Brough et al.[27] found house dust dose-dependent peanut sensitization in patients with FLG mutations, and the impact of developing allergy was greater in children with AD[28] and in children with egg allergy.[29]These observations supported a role for the "outside-in" process of food sensitization where exposure to environmental peanut in an individual with skin barrier dysfunction leads to enhanced FA.

The "inside-out" process implicates the immune response in making the skin barrier more susceptible to skin epithelial dysfunction, development of AD, and allergen entry. The current understanding of 'AD's pathogenesis is centered on the robust activation of Type 2 (IL-4, IL-13, IL-31) and Type 22 (IL-22) cytokine axes in both skin and serum.[25,30-34]Model systems showed that type 2 cytokine activation inhibits keratinocyte terminal differentiation products (i.e., filaggrin, loricrin), tight junctions (i.e., claudins), and lipid products.[35-38] Recent findings show that Th2 cytokines decrease antimicrobial peptides, causing AD skin to be more prone to colonization of infectious organisms, such as *S. aureus* . Thus, IL-4 and IL-13 play a hallmark role in the Th2 immune response in AD, contributing to both immune activation and skin barrier dysfunction. IL-31, another Th2 cytokine, has been shown to interact synergistically with IL-4, driving pruritus and contributing to the inflammatory and barrier defects of AD.[39-44] The Th22 axis also plays a role in suppressing the epidermal barrier and the lichenification and increase of S100As in chronic AD lesions.[45,46]Additional proinflammatory axes, including Th17, are preferentially upregulated in certain AD populations, such as Asians and children, revealing the heterogeneous nature of AD across its subtypes.[47-51]Recently, minimally invasive studies of the skin using tape strips, performed in infants, children and adults with moderate-to-severe AD, show robust upregulation of type 2 and 22 T-cell immune cytokines in both lesional and non-lesional AD skin.[52-54] The upregulation of immune markers in involved and uninvolved skin showed high correlations with disease severity scores and the functional barrier measure trans-epidermal-water-loss (TEWL).[55-57]

Allergic disease development is associated with a Th2 cell-mediated inflammatory response[58,59]described above. Allergic disease is preceded by the formation of specific IgE (sIgE) antibodies against environmental and food allergens, also known as the sensitization phase. In epicutaneous sensitization, specific resident dendritic cell (DC) subsets residing in the skin[60] sample antigens and present to naïve $CD4^+$ T cells in draining lymph nodes This promotes differentiation into allergen-specific $CD4^+$ T cells favouring B cell isotype class switching to sIgE cells further driving the production of IgE memory B cells[61]. Through the maturation and production of plasma cells, large amounts of sIgE antibodies are produced. The sensitization phase drives the production of a large memory pool of allergen-specific B cells and Th2 cells.

The sensitization phase is followed by the effector phase, which is triggered by subsequent exposure to previously sensitized allergens. This causes cross-linking of sIgE bound to receptor FcεRI on sensitized mast cells and basophils. Activation of these cells leads to the release of inflammatory mediators triggering an allergic reaction[62]. The immune mechanisms linking the skin and gut have their origins in skin injury-induced release of IL-33 from keratinocytes, leading to intestinal mast cell hyperplasia and food-induced anaphylaxis in mice.[63] IL-33 blocking antibodies have also been shown to prevent peanut allergy induced anaphylaxis.[64]

Interestingly, skin sampling in patients with peanut allergy but not AD reveals low filaggrin levels but increased long-chained lipid species, which may protect the skin from dryness and AD.[65] Other risk factors have been associated with peanut allergy, including filaggrin mutations, severe infantile AD, environmental irritant exposures such as detergents and *S. aureus* colonization on the skin.[66-68]

Skin dysbiosis, often observed among individuals with AD, is often characterized by reduced microbial

diversity and the presence of one or few dominant microbes. The loss of commensal microbes is likely due to several factors including host genetics, local immune response, environmental factors such as pH, temperature, humidity, hygiene practice and exposure to antibiotics. It is estimated that 30% to 100% of individuals with AD are colonized by S. *aureus* , a dominant pathogen implicated in this disease (Figure 5a).[69] *S. aureus*affects the development of both innate and adaptive immune responses. It can lead to uncontrolled inflammation by inducing lymphocyte and macrophage activation. The increased presence of *S. aureus* in the dermis directly correlates with a Th2 response evident by increased expression of IL-4, IL-13, IL-31 and TSLP.[70] These Th2 cytokines in turn suppress the production of antimicrobial peptides (AMPs) by the skin that inhibits *S. aureus*proliferation.[71]Therefore, it is not surprising that colonization by *S. aureus* is associated with increased AD severity and treatment thereof has been shown to decrease disease severity.[72,73]

Malassezia spp., previously known as Pityrosporum, is a genus of lipophilic yeast. Its role in AD's pathogenesis was initially speculated when some AD patients responded to topical and systemic antifungal therapies.[74-78] A large population study showed more than 40% of children with seborrheic dermatitis during early childhood will develop AD later on, suggesting early sensitization of seborrheic skin may result in the onset of AD.[79] Most of the Malassezia species lack fatty acid synthases genes, therefore relying on exogenous fatty acid sources that are abundant at certain cutaneous sites such as the head, neck and skin folds (Figure 5b).[80] Although the pathogenesis of *Malassezia spp* in AD is not entirely clear, yeast is known to trigger a multitude of immune responses. It is estimated that 80% of adults with AD have detectable *Malassezia* IgE antibodies.[81-83]*Malassezia spp.* in the epidermis and dermis, can be recognized by keratinocytes and Langerhans cells as well as dermal DCs. These antigen presenting cells in turn activate downstream immunologic cascades that lead to the release of proinflammatory cytokines such as TNF-alpha, IL6, IL-8, IL-10, and IL-12p70. Induced expression of TLR2 and TLR4 on human keratinocytes and DCs upon exposure to *Malassezia spp.* have been observed, suggesting direct activation of innate immune response.[84,85]In addition, the NLRP3 inflammasome in skin DCs can also be activated by*Malassezia spp* with subsequent release of Th2 cytokines (e.g., IL-1beta, IL-4, 5, 13,) likely directly contributing to AD pathogenesis.[86,87]

Lamellar bilayer structural integrity is highly organized in normal skin, seen under electron microscopy, but very abnormal in those with AD and peanut allergy. The epidermis in AD with peanut allergy is associated with high TEWL, high type 2 immune activation, *S. aureus* colonization, reduced filaggrin breakdown products, and a reduced proportion of long-chained lipid products. These observations suggest that a defective skin barrier in patients with AD and peanut allergy may predispose affected individuals to epicutaneous allergen sensitization. The availability of minimally invasive skin tape sampling techniques may play an important role in identifying infants with early epidermal barrier dysfunction who may benefit from timely initiation of novel therapies for skin barrier dysfunction, non-lesional immune activation, and microbial dysbiosis. Using this technique epidermal profiling of lipids, proteins, and transcriptome identifies differences in the epidermis between patients with peanut allergy and AD versus AD alone.[65,88]

Barrier protection is the cornerstone of AD management. Skin hydration and prevention of TEWL are keys in maintaining skin barrier homeostasis. Animal studies also suggest that changes in hydration and corneocyte adhesion within stratum corneum affect the development and maturation of epidermis.[89] Although there has been considerable controversy about whether early application of skin emollients can prevent AD and FA,[20] these studies have often not targeted high-risk infants with pre-existing evidence for skin barrier dysfunction, or the ingredients of emollients has not been optimized for infant skin barrier repair. The use of topical steroids to prevent AD flares and control subclinical inflammation is being evaluated as a potential strategy to prevent FA in AD.[20] Other novel pathogenesis-based topical and systemic therapies targeting inflammation of the skin have also been investigated for their roles in preventing FA.[90]

Petrolatum, a non-physiologic mineral lipid, is often considered a gold standard ointment-based emollient that can prevent TEWL effectively for 4-6 hours. Therefore, to maintain optimal skin hydration, ointment-based emollients should be applied 3 to 4 times daily to provide complete protection. However, ointment-based emollients can also exacerbate AD; therefore, alternatives must be considered. Lipids including ce-

ramide, fatty acids and cholesterol are mixed in appropriate ratio within stratum corneum to maintain its integrity.[91,92]Atopic skin is known to be deficient in lipids especially ceramide and hygroscopic amino acids that are the result of filaggrin breakdown products.[93,94]Newer generations of emollients containing these lipids have been developed in recent years.[95,96]A recent study demonstrated a trilipid cream was more effective than a paraffin-based emollient in reducing TEWL and sIgE levels.[20,97]However, efficacy in AD or FA prevention is yet to be proven in a randomized clinical trial.[98] While treating AD patients with a barrier-based approach, a liver X receptor agonist upregulated terminal differentiation and lipid products in the skin of patients with AD, consistent with its mechanism of action;[99] however, it was not associated with clinical benefit or suppression of immune products (Th17/Th22/IL6). This suggests that although barrier-based approaches may be valuable for disease prevention, the immune abnormalities perpetuate the AD disease phenotypes and should be targeted to resolve active AD.

The discovery of cytokine dysregulation in non-lesional skin from AD patients suggest the role of systemic therapy especially for individuals with severe disease. The increased understanding of AD's immune pathogenesis led to the development of immune-based treatments targeting Th2 cytokines.[100-105]Downregulation of immune markers in the skin of patients treated with such agents highly correlated with reductions in disease severity scores, demonstrating clinical improvement.[33,106-111]Furthermore, the Th2-targeting anti-IL-4R mAb dupilumab was shown to induce significant changes in the microbiome of skin lesions, again supporting the key role of the Th2 cytokines in inducing the disease pathogenesis.[112]

Dietary factors

The obvious dietary factor relevant to the establishment of oral tolerance (and susceptibility to FA) is **food allergens** . Oral tolerance is the active maintenance of both mucosal and systemic non-responsiveness to ingested food allergens.[113] The induction of tolerance to dietary antigen is a multistep process;[114]**dietary vitamin A** plays a critical role in its regulation. $CD103^+$ dendritic cells (DC) in the gut associated lymphoid tissue (GALT) express elevated levels of retinal dehydrogenase (RALDH) enzymes which enhance their ability to metabolize dietary vitamin A. Antigen-loaded $CD103^+$ DC migrate to the mesenteric lymph node (MLN) from the intestinal lamina propria (LP). Retinoic acid (RA) produced by these DC and by stromal cells in the MLN induce the expression of the gut homing receptors CCR9 and $\alpha4\beta7$ favoring TGF-β dependent conversion of $Foxp3^+$ regulatory T cells (Tregs). [115-117]Committed Tregs then home back to LP, expanding under the influence of IL-10 produced by $CX3CR1^{hi}$ macrophages. Some Tregs exit the mucosa via the lymph or bloodstream to promote systemic tolerance. [114] Elegant studies in germ-free mice on an antigen-free diet showed that, in the small intestine, $Foxp3^+$ Tregs are induced by exposure to dietary antigen.[118]In the large intestine, however, $Foxp3^+$ Tregs are induced by a subset of the mucosa-associated bacteria which comprise the intestinal microbiota.[119]

The increasing prevalence of FA parallels increases in other non-communicable diseases and can be explained, in part, by alterations in the composition and function of the commensal microbiome. 21^{st} century lifestyle practices including increased antibiotic use, low fiber/high fat diets, reduced exposure to infectious diseases, Caesarean birth and formula feeding have collectively depleted populations of bacteria beneficial to health.[120-122] In addition to dietary antigen induced $Foxp3^+$ Tregs, a bacteria-induced barrier protective response is required to prevent allergic sensitization to food.[123,124]Clostridia-induced IL-22 production by type 3 innate lymphoid cells (ILC3) is necessary and sufficient to reduce intestinal epithelial permeability to dietary allergen.[123] IL-22 protects the intestinal epithelial barrier by regulating epithelial proliferation and the production of mucus and anti-microbial peptides.[124] The mechanisms by which intestinal bacteria, particularly those in the Clostridia class, regulate mucosal immunity and allergic disease are increasingly understood. Prominent among these is their ability to ferment short chain fatty acids (SCFAs) from dietary fiber. SCFAs have potent immunomodulatory effects correlated with host health[125] including induction of colonic Tregs[126] and improvement of allergy symptoms in a mouse model.[127] Butyrate, in particular, is an important energy source for colonic epithelial cells.[128] Butyrate drives oxygen consumption by colonocytes through β-oxidation, which maintains a locally hypoxic niche for butyrate-producing obligate anaerobes .[129] Early dysbiosis characterized by an impaired capacity to produce butyrate may be a common feature of

allergic diseases.[130]**Tryptophan metabolites** , from both dietary and bacterial sources, also play a central role in regulating tolerance in the gut. Catabolism of tryptophan to indole derivatives produces ligands which bind to the aryl hydrocarbon receptor on innate lymphoid cells (ILC3) and stimulate the production of IL-22 to regulate epithelial barrier permeability. [131]Finally commensal bacteria can metabolize **bile acids** to produce bioactive mediators which regulate T cell differentiation in the intestinal lamina propria (Figure 6).[132]

From the evidence from mouse models that food allergen exposure was necessary for the development of tolerance, observational studies in humans linking allergen avoidance in the first few years of life with the development of FA further supported the dual allergen-exposure hypothesis. Specifically, a cross-sectional study showed that peanut consumption in Israel early in life was associated with a lower prevalence of peanut allergy than a population with a similar ancestry in the UK, where peanut was typically avoided in the first few years of life.[133] Whereas avoidance of food allergens in an infant's diet was standard advice in many countries, advice has changed, and oral tolerance induction is being used as a strategy to prevent peanut and other FA by introducing peanuts and other food allergens early into the diet of young infants.[17] The LEAP study showed that the rate of peanut allergy could be reduced by 86% in non-sensitised children and the LEAP-On study confirmed that this protection against peanut allergy remained one year after complete subsequent avoidance at five years of age in the children's diet.[134] The impact of early peanut introduction in LEAP was peanut specific and did not protect against other FA.[135] The EAT study (a lower risk, exclusively breastfed population) showed similar results for peanut in a per protocol analysis.[136] It also showed that consuming cooked egg in infancy was associated with a reduction in egg allergy. Since, subsequent studies and a meta-analysis have confirmed the efficacy of this approach,[133,137-139]and a recent Japanese study has shown that early introduction of cow's milk in early infancy protects against the development of milk allergy.[140]Introducing multiple foods early and continuing to eat them regularly proved challenging for most families in the EAT study. The study identified several factors associated with reduced adherence to this strategy: increasing maternal age, feeding difficulties in the neonate, and non-Caucasian ethnicity. This could help identify families who might benefit from further support to encourage early weaning. [141-143]

Many other dietary factors have been studied for their association with FA and/or AD. Observational studies have been summarized in a number of systematic reviews focusing on the maternal and infant diet[144,145]or the maternal diet during pregnancy alone.[144,146]Collectively over a hundred papers from observational studies have been identified reporting dietary patterns, diet diversity, fruit and vegetable intake, fat and fatty acid intake, vitamin and mineral intake, and a wide range of other dietary exposures, including alcohol, tea or coffee intake. Summarizing these studies using meta-analysis is limited as study exposures and outcome definitions are highly heterogeneous. A comprehensive review by the UK Food Standards Agency focusing on maternal and infant dietary intake concludes that there is no consistent evidence for associations between dietary exposures and allergy outcomes based on observational studies.[144] Other systematic reviews have, however, attempted to summarize findings from these studies.

Dietary patterns and food groups

Dietary patterns, such as the Mediterranean diet, have not been associated with reduced AD or FA in offsprings. During pregnancy,[145] no studies report on maternal dietary patterns in lactation and AD or FA outcomes in the infant. However, two systematic reviews tentatively conclude that fruit, vegetable, and yogurt intake in pregnancy may prevent offspring AD and that margarine and vegetable oil may increase the risk of AD.[144,146]Studies of the associations between intake of particular foods and infant FA are lacking[146] Diet patterns in infancy have not been associated with infant AD. One study indicates that a diet pattern of predominantly home-cooked food may prevent FA. [147]

Diet diversity

Diet diversity is the number of different foods, food groups or food allergens eaten over time, such as the first year of life. Recently there has been considerable interest in the effect of infant diet diversity in preventing allergic diseases. A task force report from the European Academy of Allergy and Clinical Immunology

(EAACI)[148] suggested that increased diet diversity in infancy may reduce the risk of developing allergic diseases such as asthma, AD, allergic rhinitis or FA in later childhood. Two observational studies, have shown increased diet diversity in the first year of life to be associated with reduced FA by six[147] and ten[149] years. Using data from Europe and the UK, these observational studies suggest that early oral intake of a variety of foods and food allergens, once the infant is developmentally ready, may reduce the incidence of FA in the first 10 years of life. Studies focusing on diet diversity in infancy and AD in childhood are however less clear. One study found both an increased risk and no effect on AD outcomes at different timepoints.[150] Another study reported a preventative effect and no effect at different time points.[150,151]Three studies found both an increased risk[152,153]and a preventative effect[154-156] of increased diet diversity on AD outcomes in childhood.

Vitamins and minerals

Vitamin D insufficiency and deficiency have been associated with IgE sensitization[157] and FA in some studies[158]but not others.[159]There is little evidence from interventional studies of vitamin D supplementation for primary allergy prevention[160-163] as reviewed by Yepes-Nunez, et al.[164] The lack of evidence about the role of vitamin D in FA risk is in part related to the multiple factors influencing vitamin D levels that need to be accounted for when designing studies. These factors include sun exposure, country and latitude of residence, migratory status, skin colour, ethnicity, age, diet, vitamin D supplementation (timing, formulation and dose), genetic polymorphisms affecting metabolism, epigenetic changes contributing to vitamin D levels, vitamin D binding protein, interaction with disease-associated genetic polymorphisms (e.g., ORMDL3), definition of vitamin D insufficiency/deficiency, and time-points to assess levels (longitudinal versus cross-sectional)[165].

One systematic review indicated that intake of beta-carotene, vitamin E, zinc, calcium, magnesium, and copper during pregnancy might be protective of offspring AD[146]. This review also summarized a small number of papers indicating that copper and vitamin C intake during pregnancy may reduce the risk of offspring FA. In contrast, vitamin D intake was associated with an increased risk of offspring FA. The amount of vitamins and minerals taken in these studies did not align with healthy eating guidance, and the results should be interpreted with caution[146].

Results from RCTs have been summarized in several guideline papers and systematic reviews, with or without meta-analysis, to guide families. Results from these meta-analyses largely support current recommendations from the American Academy of Pediatrics (AAP),[166]EAACI,[17] and the consensus statement from the 3 North American allergy societies.[16] All refrain from making recommendations on omega-3 fatty acids, vitamins, minerals, or pre-/pro-/syn-biotics for allergy prevention.

Conclusions

The 2000 AAP policy[167] recommended avoidance of allergenic foods for breastfeeding mothers and delayed introducing allergenic foods to infants to prevent FA was based on expert opinion informed by a limited number of low quality studies.[168] These guidelines influenced infant feeding practices for almost 20 years,[169] while FA only continued to increase, rather than decrease. These guidelines were reversed in 2008, but not replaced with comprehensive guidelines, only limited recommendations.[168]With publication of data from higher-quality studies, recent guidelines offer a comprehensive approach to maternal/infant diet.[16,17,166,170]The foundation for these studies and ongoing efforts to study the prevention of atopy was laid throughout the 1900s by pioneers in the field (Table 1).

It is critical to not only have consistent diagnostic criteria for the conditions being studied, but also to have comparable outcomes that are patient-relevant when possible. This will allow for valid and complete comparisons across studies in diverse populations, including high and general risk populations, regionally and globally. Reliable estimates of the global burden of atopic disease and improved epidemiologic data for these conditions is crucial to gain support for and acceptance of prevention guidelines.

Interventions to prevent AD and FA targeted at the first few months of life are not early enough for some babies. There are likely factors already in place within the first few weeks of life, or earlier, particularly

in at-risk infants who may start the march towards atopy and a Th2 milieu in the womb. The proposed increased risk for FA with more than daily application of moisturizer in the EAT study cohort highlights the need for earlier assessments and interventions among diverse and representative populations employing consistent disease definitions using easily applied and clinically relevant assessments.[171] This finding further cautions against drawing potentially premature conclusions when important confounders cannot be adequately accounted for. These most recent findings add to the conflicting evidence about the potential to prevent AD to reduce the risk of FA.[172] Further, this supports the need for intervention trials designed from the outset to study FA using a broadly accepted definition as the primary outcome, beginning in the first weeks of life, with intentionally developed treatment groups and carefully planned assessments in hopes of Stopping Eczema and ALlergy (SEAL, NCT03742414). The SEAL Study will also attempt to answer ongoing research questions identified in this review, summarized in Box 1.

It is unlikely that there is a single way to stop the atopic march once underway or a master switch that could render all the external factors discussed in this review ineffective at inducing a Th2 response. It remains important to investigate these potential targets for prevention (Figure 7) and continue to search for others. Given the remarkably conflicting results within and between studies on the microbiome and a wide variety of dietary factors, it seems that well-informed guidelines in these areas are farther off in the future, and may require extensive public health campaigns to slowly change behaviors if successful approaches can be identified.

It is of course still necessary to provide recommendations before definitive evidence that is applicable to diverse populations is available. In the interim, recent updates from North America[16] and the UK[17] are more unified and coming aligned with those from Australasia.[170] There will certainly be disagreement with some aspect of any guideline, but these do represent a responsible approach toward prevention of atopic conditions, based on the presently limited evidence base. Well-designed trials must continue, and future trials move forward in the face of unprecedented challenges faced today by study subjects, clinical researchers, and scientists so that the field can move closer to an understanding of the complex mechanisms driving allergic sensitization early in life. Effective strategies for the prevention of atopic conditions, particularly AD and FA will almost certainly be the result.

Table 1A*: Major Milestones Laying the Foundation for Prevention Studies*

Topic	Year (reference)	Study or Publication Title	Author(s)	Key Findings and Contributions to Allergy	Notable Limitations	Study Population	Study Type	Level of Evider
Ancient Maternal Dietary Avoidance	2735-2598 BC[174]	*Interdictions Concerning Foods*	Chinese emperors Shen Nong and Huang Di	Advised pregnant women to avoid shrimp, chicken, meat, and other agents incriminated in skin lesions	Ancient Chinese History, lacking detailed methods	Ancient Chinese	The first known official guideline recommending food avoidance to prevent disease, via Emperor's decree	n/a

Topic	Year (reference)	Study or Publication Title	Author(s)	Key Findings and Contributions to Allergy	Notable Limitations	Study Population	Study Type	Level of Evidence
Defining a Disease and a Medical Specialty	1906[175]	*Allergy*	von Pirquet C	*"For this general concept of a changed reactivity I propose the term Allergy. 'Allos' implies deviation from the original state, from the behaviour of the normal individual, as it is used in the words Allorhythmia, Alloptropism."*	Opinion	n/a	Clinical observations	n/a
Oral Tolerance Induction	1908[176]	*A case of egg poisoning*	Schofield AT	First modern oral desensitization for food allergy		London clinic patient	Case Report	Level 5

Topic	Year (reference)	Study or Publication Title	Author(s)	Key Findings and Contributions to Allergy	Notable Limitations	Study Population	Study Type	Level of Evider
Diagnosing Food Allergy and Inducing Oral Tolerance	1912[177]	*A case of allergy to common foods*	Schloss OM	The early development of food extracts for scratch testing; identification of ovomucoid as the major egg allergen and its use for oral desensitization	Single case	New York clinic patient	Case report	Level 5
The Concept of Immunoglobulin E	1921[178]	The Prausnitz-Kustner Test	Prausnitz O & Kustner H	Demonstrated passive sensitization of the skin in health subjects by transferring serum from a sensitized individual using the PK test		Prausnitz (tolerated fish) & Küstner (allergic to fish)	Mechanistic	Level 5

Topic	Year (reference)	Study or Publication Title	Author(s)	Key Findings and Contributions to Allergy	Notable Limitations	Study Population	Study Type	Level of Evider
Diagnosing Food Allergy	1950[179]	*Allergy for corn and its derivatives: experiments with a masked ingestion test for its diagnosis*	Loveless MH	Amid widely varying reports of the incidence of corn allergy, recognized that positive tests and patient histories often do not match a "blindfold test," and appealed for standardized FA testing		Survey of American Academy of Allergy members, case series from US allergy clinics	Case series and cohort	Level 4

Topic	Year (reference)	Study or Publication Title	Author(s)	Key Findings and Contributions to Allergy	Notable Limitations	Study Population	Study Type	Level of Evidence
The Discovery of IgE	1966-8[180,181]	*Immunoglobulin E, a new class of human immunoglobulin*	K & T Ishizaka; Johansson SGO & Bennich H	The search for reagin concludes with the nearly simultaneous identification of IgE, the critical component of an immediate hypersensitivity reaction	The IgE receptor, discovered a few years later, confirmed the effector functions of IgE	Myeloma cell lines	Mechanistic	Level 4

Topic	Year (reference)	Study or Publication Title	Author(s)	Key Findings and Contributions to Allergy	Notable Limitations	Study Population	Study Type	Level of Evider
Diagnosing Food Allergy	1976[182] 1988[183]	*Objective clinical and laboratory studies of immediate hypersensitivity reactions to foods in asthmatic children; Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure*	May CD, Bock SA, et al.	The gold-standard of diagnosis, the double-blind, placebo-controlled oral food challenge was described and became more accessible to the practicing allergist; defined a SPT <3mm SPT as negative		US asthma center	Cohort	Level 4

Topic	Year (reference)	Study or Publication Title	Author(s)	Key Findings and Contributions to Allergy	Notable Limitations	Study Population	Study Type	Level of Evider
Mechanisms of Sensitization	1996[184]	The dual exposure hypothesis	Lack G & Golding J	"Avoidance measures would serve only to reduce exposure to peanuts to low levels, and this could paradoxically increase allergic sensitisation to peanuts: low dose exposure to allergens favors production of IgE, and as little as 1 μg of inhaled allergen a year may be sufficient to induce allergic sensitization vias the airways."	Opinion, observed less peanut allergy in some cultures outside Britain that also frequently consumed peanut		n/a	Level 5

Topic	Year (reference)	Study or Publication Title	Author(s)	Key Findings and Contributions to Allergy	Notable Limitations	Study Population	Study Type	Level of Evider
Diagnosing food allergy	1997[185] & 2001[186]	Food-specific IgE values predict OFC outcomes	Sampson HA & Ho DG; Sampson HA	Proposes and validates predictive values or cut-offs, guiding the decision to perform an OFC	Highly atopic population, at high risk for FA	US tertiary care, academic allergy clinic	Cohort	Level 4

Topic	**Year (reference)**	**Study or Publication Title**	**Author(s)**	**Key Findings and Contributions to Allergy**	**Notable Limitations**	**Study Population**	**Study Type**	**Level of Eviden**
At the time of publication of most of these milestones, the existence of food allergy was questioned by many in the medical community, including most allergists. Despite how remarkable and significant these achievements were for the field of allergy and immunology, it was not until the end of the 20th century that food allergy as a field began to over-	At the time of publication of most of these milestones, the existence of food allergy was questioned by many in the medical community, including most allergists. Despite how remarkable and significant these achievements were for the field of allergy and immunology, it was not until the end of the 20th century that food allergy as a field began to over-	At the time of publication of most of these milestones, the existence of food allergy was questioned by many in the medical community, including most allergists. Despite how remarkable and significant these achievements were for the field of allergy and immunology, it was not until the end of the 20th century that food allergy as a field began to over-	At the time of publication of most of these milestones, the existence of food allergy was questioned by many in the medical community, including most allergists. Despite how remarkable and significant these achievements were for the field of allergy and immunology, it was not until the end of the 20th century that food allergy as a field began to over-	At the time of publication of most of these milestones, the existence of food allergy was questioned by many in the medical community, including most allergists. Despite how remarkable and significant these achievements were for the field of allergy and immunology, it was not until the end of the 20th century that food allergy as a field began to over-	At the time of publication of most of these milestones, the existence of food allergy was questioned by many in the medical community, including most allergists. Despite how remarkable and significant these achievements were for the field of allergy and immunology, it was not until the end of the 20th century that food allergy as a field began to over-	At the time of publication of most of these milestones, the existence of food allergy was questioned by many in the medical community, including most allergists. Despite how remarkable and significant these achievements were for the field of allergy and immunology, it was not until the end of the 20th century that food allergy as a field began to over-	At the time of publication of most of these milestones, the existence of food allergy was questioned by many in the medical community, including most allergists. Despite how remarkable and significant these achievements were for the field of allergy and immunology, it was not until the end of the 20th century that food allergy as a field began to over-	At the time of publication of most of these milestones, the existence o food allergy was questioned by man in the medical community, including most al lergists. Despite how remarkable an significant these achievements were fo the fiel of allergy and immunology, it was not until th end of the 20th century that food allergy as a field began to over-

Topic	**Year (reference)**	**Study or Publication Title**	**Author(s)**	**Key Findings and Contributions to Allergy**	**Notable Limitations**	**Study Population**	**Study Type**	**Level of Evider**

Table 1B*: Major Milestones in Studying the Prevention of Atopy*

Area of Focus	Year (Reference)	Study Name or Publication Title	Author	Key findings or recommendations	Notable limitations	Population Studied	Type of Study	Level of Evidenc
Cutaneous Sensitization	1994[190]	Increased airways responsiveness in mice depends on local challenge with antigen	Saloga J, et al.	First evidence to support that sensitization could occur through skin	Murine skin differs from human skin	Murine model	Mechanistic	Level 5
Cutaneous Sensitization	2003[191]	Avon Longitudinal Study of Parents and Children (ALSPAC)	Lack G, et al.	Peanut allergy associated with topical use of peanut oil infants, but not with maternal consumption		UK, general population	Population-based, longitudinal birth cohort	Level 2

Area of Focus	Year (Reference)	Study Name or Publication Title	Author	Key findings or recommendations	Notable limitations	Population Studied	Type of Study	Level of Evidence
The Role of Filaggrin in AD	2006[93]	*Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis*	Palmer CNA, et al.	AD was more common in homozygous or compound heterozygous for FLG null alleles, and nearly absent in those without	Only 2 mutations had been identified and analyzed, both common in those of European ancestry, but rare in other ethnicities	9 Irish families with ichthyosis vulgaris and/or AD; 2 cohorts of Scottish children with and without asthma; Danish children from the COPSAC study	Multiple cohorts	Level 2

Area of Focus	Year (Reference)	Study Name or Publication Title	Author	Key findings or recommendations	Notable limitations	Population Studied	Type of Study	Level of Evidence
The Role of Filaggrin in FA	2011[66]	*Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy*	Brown SJ, et al.	FLG loss-of-function mutations significantly increase the risk of peanut allergy, suggesting a role for epithelial barrier dysfunction	Different definitions of AD and criteria for diagnosing peanut allergy were used in the different populations; difficult to distinguish the role of AD from FLG status, and other variables affecting the development of peanut allergy; the effect varied in different populations despite all being predominantly white and of European ancestry	English, Dutch, and Irish subjects with peanut allergy and controls; replicated in a white, Canadian case-control population	Case-control study	Level 3

Area of Focus	Year (Reference)	Study Name or Publication Title	Author	Key findings or recommendations	Notable limitations	Population Studied	Type of Study	Level of Evidence
Skin barrier Dysfunction and Transcutaneous Sensitization in FA	2014[27]	*Peanut allergy: Effect of environmental peanut exposure in children with filaggrin loss-of-function mutations*	Brough HA, et al.	Exposure to peanut protein in household dust demonstrated a dose-response relationship with measures of peanut sensitization and allergy at 8 and 11y in children with FLG mutations, when controlling for other factors; no effect of exposure was seen in children with WT-FLG	Peanut allergy not challenge-proven in all subjects; overall small number of subjects with peanut allergy, FLG gene status, and exposure history; excluded non-Caucasians as the 6 FLG mutations studied were only defined in Caucasians	UK, high risk infants (family history of atopy)	Observational study within randomized controlled study	Level 3

Area of Focus	Year (Reference)	Study Name or Publication Title	Author	Key findings or recommendations	Notable limitations	Population Studied	Type of Study	Level of Evidenc
Topical intervention for AD	2014[192]	Application of moisturizer to neonates prevents development of atopic dermatitis	Horimoku K, et al.	Daily application of an emulsion-based moisturizer starting at 1week of life prevented AD in 1/3 of infants at 8m	Control group could use petroleum jelly if desired, which may be beneficial for SB, limiting the impact of the intervention	Japan, high risk	RCT	Level 2
Oral Tolerance Induction	2015[193] & 2016[194]	LEAP & LEAP-On	du Toit, et al.	Early introduction and regular consumption of peanut in infants at high risk for FA prevents peanut allergy, and likely induces durable, and long-lasting tolerance	Excluded infants with peanut SPT>4mm at entry	UK, high risk cohort	Randomized, open-label, controlled trial	Level 2

Area of Focus	Year (Reference)	Study Name or Publication Title	Author	Key findings or recommendations	Notable limitations	Population Studied	Type of Study	Level of Evidenc
Preventative Emollient Therapy for AD and FA	2018[195]	A randomised trial of a barrier lipid replacement strategy for the prevention of atopic dermatitis and allergic sensitisation: The PEBBLES Pilot Study	Lowe AJ, et al.	Twice daily application of emollient rich in ceramides to infants in the first 3weeks of life through 6m demonstrated a trend towards less AD and food sensitization at 12month; infants who had emollient applier BID for at least 5/7 day per week did have a significant reduction in food sensitization	Food sensitization only assessed at 1y, not later in life and not challenge-proven; Small n=80), pilot study.	Australia, high risk infants (parental history of atopy)	Pilot randomized, parallel, single-blind, controlled trial	Level 3

Area of Focus	Year (Reference)	Study Name or Publication Title	Author	Key findings or recommendations	Notable limitations	Population Studied	Type of Study	Level of Evidence
Assessing Skin Barrier Dysfunction	2019[196]	The nonlesional skin surface distinguishes atopic dermatitis with food allergy as a unique endotype	Leung DYM, et al.	Using a non-invasive, well-tolerated skin tape stripping method, identifies unique immature skin barrier characteristics in the stratum corneum that distinguish between children with AD and FA (AD+FA+) from those with AD but without FA (AD+FA-)	Results require validation in larger, diverse populations with challenge-proven allergy to a variety of foods, not just peanut	62 US children classified as AD+FA+, AD+FA- or controls	Blinded, prospective mechanistic study	Level 3

Area of Focus	Year (Reference)	Study Name or Publication Title	Author	Key findings or recommendations	Notable limitations	Population Studied	Type of Study	Level of Evidence
Proactive Early AD Treatment and the Prevention of FA	2019[197]	Prevention of Allergy via Cutaneous Intervention (PACI) pilot	Miyaji Y, et al.	Earlier aggressive treatment of AD shortened its duration in infants, and resulted in fewer food allergies at 2 years of life	Smaller, retrospective pilot study; cohorts had significant differences in baseline characteristics	Japan	Retrospective cohort	Level 4

Area of Focus	Year (Reference)	Study Name or Publication Title	Author	Key findings or recommendations	Notable limitations	Population Studied	Type of Study	Level of Evidence
Preventative Emollient Therapy for AD and FA	2020[198]	Barrier Enhancement for Eczema Prevention (BEEP)	Chalmers JR, et al.	No evidence for prevention of AD at 2y with daily emollient use, but possible slight increase in infection risk, and non-significant increase in FA (largely to egg) in the intervention group	Choice of emollient; limited FA assessment; median time to initiation of skin care at 11 days of life	UK, high risk	Pragmatic, parallel group RCT	Level 2

Area of Focus	Year (Reference)	Study Name or Publication Title	Author	Key findings or recommendations	Notable limitations	Population Studied	Type of Study	Level of Evidence
Oral Tolerance Induction	2020[199]	Preventing food allergy in infancy and childhood	de Silva D, et al.	Early introduction of cooked egg (not raw or pasteurized egg) likely helps prevent egg allergy; avoiding supplementation with cow's milk-based formula in the first week of life may slightly reduce milk allergy; nearly every other dietary intervention reviewed has little to no effect	Many are small studies of lower certainty of evidence, findings need to be validated in large, heterogeneous populations	n/a	Systematic review with meta-analysis	Level 2

Area of Focus	Year (Reference)	Study Name or Publication Title	Author	Key findings or recommendations	Notable limitations	Population Studied	Type of Study	Level of Evidence
Preventative Emollient Therapy for AD and FA	2020[200]	Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL)	Skjerven HO, et al.	Found no decrease in AD or FA at 12m with skin emollient use, early complementary feeding or both	Skin intervention started at 2 weeks of life using a bath oil and cream; early food introduction began with peanut butter at 3m; overall poor adherence in the intervention groups; low statistical power to assess FA (results for FA at 3y forthcoming)	Scandinavian standard risk birth cohort	Prospective interventional, cluster-randomized controlled trial	Level 2

Area of Focus	Year (Reference)	Study Name or Publication Title	Author	Key findings or recommendations	Notable limitations	Population Studied	Type of Study	Level of Evidenc
Link between Emollient use and Food Allergy	2021[171]	Association of frequent moisturizer use in early infancy with the development of food allergy	Perkin M, et al.	Observed an increased risk of food allergy with the application of moisturizer more frequent than once daily	All but 1 case of FA developed in children with at least 1 atopic parent; AD assessed at 3m enrolment visit only; the cohort frequently used oils for baby massage, which may prevent formation of an intact skin barrier; unable to control for some potential confounding factors	UK, exclusively breastfed standard risk cohort enrolled in the EAT study and randomized to standard vs early introduction of 6 foods with poor protocol adherence	Retrospective analysis of questionnaire data	Level 3,

Box 1: Topics for future research

- Definitions of disease that are easy to apply, widely accepted and clinically relevant
- Accurate estimates of the global epidemiologic burden of atopy
- Incorporate patient-relevant outcomes for food allergy and AD into trial designs
- Earlier timing of interventions to address skin barrier dysfunction (SBD)
- Randomized trials focusing on maternal and early life nutrition with robust measurements of food, macro and micronutrient intake and clearly defined study outcomes
- Current efforts should be broadened to more fully understand the mechanisms underlying initiation, maintenance, loss, and redevelopment of tolerance
- Fully characterize the molecular mechanisms underlying the phenotypes of SBD that place some, but not all patients with AD at a significantly increased risk for atopy, particularly food allergy
- Distinguish other SBD phenotypes, as seen in seborrheic dermatitis and psoriasis from those in AD identifying potential targets to maintain tolerance later in life
- Identify targeted treatment approaches to heal the SBD associated specifically predisposing to atopy

- Ongoing evaluation of environmental exposures including irritants, pollution, pollen, bacteria, viruses and fungi
- Begin to better understand the complex interaction of the commensal microbiome of the gut and skin with potentially pathogenic bacteria and fungi
- Focus the study of environmental and microbial factors on identifying modifiable risks for manageable public health interventions benefiting the majority of the global population

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Legends:

Figure 1. Prevalence of Paediatric FA Around the World adapted from Warren C, Jiang J, Gupta

R.Epidemiology and Burden of Food Allergy. *Curr Allergy Asthma Rep.* 2020;20(2), Lyons SA,

Clausen M, Knulst AC, et al. Prevalence of Food Sensitization and Food Allergy in Children

Across Europe. *J Allergy Clin Immunol Pract.* 2020;8(8):2736-2746 e2739 and Venter C, Pereira B, Voigt K, et al. Prevalence and cumulative incidence of food hypersensitivity

in the first 3 years of life. *Allergy.* 2008;63(3):354-359.

Figure 2: Prevalence of Current Eczema Symptoms (ISAAC Phase III: Ages 6-7 adapted from Odhiambo J, Williams H, Clayton T, Robertson C, Asher M. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three.*J Allergy Clin Immunol.* 2009;124(6):1251-1258

Figure 3: Prevalence of Current Eczema Symptoms (ISAAC Phase III: Ages 13-14) adapted from from Odhiambo J, Williams H, Clayton T, Robertson C, Asher M. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three.*J Allergy Clin Immunol.* 2009;124(6):1251-1258

Figure 4: In the "outside-in" hypothesis, skin barrier defect allows penetration of allergens and

microbes leading to atopic sensitization whereas, in the "inside-out" paradigm, a polarized

immune response leads to a defective skin barrier. Adapted from Leung DY, Guttman-Yassky E.

Deciphering the complexities of atopic dermatitis: Shifting paradigms in treatment approaches.

J Allergy Clin Immunol. 2014;134(4):769-779.

Figure 5: Skin dysbiosis, especially colonization of*Staphylococcus aureus* and *Malassezia spp.,* is often seen among young children with atopic dermatitis. (a) *S. aureus*colonization on a six-month child; (b). heavy colonization of*Malassezia spp.,* also known as Pityrosporum, on the scalp of an infant.

Figure 6: Dietary compounds and their conversion by commensal bacteria influence oral tolerance. Several dietary components and digestive products contribute heavily to the function of the gut immune system. Gut-resident $CD103^{+}$ dendritic cells (DCs) directly convert dietary vitamin A to retinoic acid (RA) for further downstream immune signaling. Conversely, tryptophan, liver-derived bile acids, and fiber must first be metabolized by commensal bacteria such as Clostridia. These bacteria degrade tryptophan into several compounds that can bind to the aryl-hydrocarbon receptor (Ahr) of ILC3s, playing a role in IL-22 production. Secondary bile acids and short chain fatty acids (SCFAs), including butyrate, signal directly to epithelial cells as well as local immune cell populations residing in the lamina propria. Collectively, these compounds enhance epithelial barrier integrity by stimulating Paneth cells to produce anti-microbial peptides, goblet cells to produce mucus, and epithelial cells to produce tight junction and adherens proteins. In addition, they induce populations of tolerogenic lymphocytes such as peripherally induced regulatory T cells (iTregs) and IgA-producing plasma cells. Together, these functions are essential for the maintenance of oral tolerance.

Figure 7: Diagram of possible causal associations between genetics, skin exposures, diet leading to eczema and/or food allergy. The interplay between genetics, diet, and skin/microbiome exposure are connected by arrows showing the direction of causality hypothesized to ultimately influence food allergy. The relevant causal factors of the dual allergen exposure hypothesis are outlined by the blue rectangle. This hypothesis postulates that allergen exposure through the skin leads to the development of food allergy. The degree of a broken skin barrier involved with eczema is thought to interact with allergen exposure to increase the probability of allergy development with increasing barrier disfunction. While early introduction of food and diet diversity has been proven to prevent food allergy (dark green), other factors such as breastfeeding, commensal bacteria metabolizing bile acids, tryptophan from dietary/commensal bacterial sources, dietary fiber, vitamins, pre-pro- and syn-biotics have weaker evidence base for this (light green). Reducing eczema severity has yet to be consistently shown as a preventative causal mechanism. Nevertheless, eczema severity exists as one of the strongest predictors of food allergy, and therapies to heal a broken skin barrier remain as a leading mechanism to mediate the prevention of food allergy.