

Reviews

The skin as a target for prevention of the atopic march



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Key Messages

- Childhood allergic diseases are common and cause a substantial health burden.
- Atopic dermatitis (AD)/skin inflammation may increase risk of other allergic diseases.
- Routine use of emollients from infancy halves the risk of AD.
- Trials will determine if emollient use reduces risk of food allergy and asthma.

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ABSTRACT

Objective: Allergic diseases have increased dramatically in the developed world during the past few decades, yet the understanding of risk factors and effective prevention approaches remain limited. In this review, we summarize the evidence supporting the hypothesis that skin-barrier impairment and early-life atopic dermatitis (AD) could play a causal role in the development of sensitization and subsequent food allergies and allergic airways disease (allergic asthma and rhinitis). We further discuss the potential to target the skin barrier as a means to lower the incidence of allergic disease.

Data Sources: Review of published literature.

Study Selections: Narrative.

Results: There is a strong link between AD and sensitization, food allergy, asthma, and allergic rhinitis, particularly AD that is severe and commences in the first 6 months of life. There also is emerging evidence that regular use of prophylactic emollients can significantly decrease the expression of AD, at least while treatment continues. Studies are exploring whether decreased AD expression might modulate the allergic response at a more fundamental level and potentially alter the association between early-life AD and subsequent development of food allergy and allergic airways disease.

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Conclusion: Although at this point there is only indirect evidence that early-life emollient use might prevent AD and food allergy, early studies are encouraging. The results of high-quality prevention trials that are in progress are eagerly anticipated. If found to be effective, then neonatal emollient use could be a simple public health measure to lower the incidence of AD, food allergies, and allergic airways disease in future generations. © 2017 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

The “atopic march” is a clinical sequence that begins with atopic dermatitis (AD) and progresses to food allergy followed by subsequent development of respiratory allergies (asthma and/or allergic rhinitis).^{1,2} The increased prevalence of allergic diseases in Westernized societies during recent decades has sparked considerable interest in whether early-life intervention might prevent the evolution of the atopic march.

Allergic diseases are common in Westernized countries and cause substantial health, social, and economic burdens. There are dramatic differences between geographic areas in the prevalence of these conditions and prevalence shifts over time,³ making it difficult to provide accurate estimates of prevalence. AD, also known as atopic eczema or simply eczema, is the earliest manifestation of the atopic march and affects approximately 20% to 30% of infants.⁴ Another common and early manifestation of allergic disease is food allergy. Recent reports have suggested that food allergy affects 5% to 10% of infants in early life,^{5–7} and there has been a relatively recent and dramatic increase in the rate of hospital admissions for food-induced anaphylaxis in young children in several countries including Australia,⁸ the United Kingdom,⁹ and the United States.¹⁰ Although allergic diseases can resolve in some individuals with time, there are currently no cures for these conditions. These conditions are a major health concern, because they are the most common chronic illnesses affecting children in Western societies.

To date, most research into strategies for the prevention of allergic disease has been disappointing. Reviews covering these studies are already available for food allergy¹¹ and AD.¹² There is growing awareness of the role of epithelial barrier dysfunction in the pathogenesis of allergic disease,¹³ and there is mounting evidence that impaired skin barrier and inflammation associated with AD could be a precursor to allergic sensitization and other forms of allergic disease.¹ The strong link between AD, particularly AD that is early onset and severe, and other forms of allergic disease, including food allergies and asthma, has been well recognized for some time.^{14–16} This observation has led to the atopic march hypothesis, in which it is argued that AD might actually be a cause of the subsequent increase in risk of food allergy and allergic respiratory disease. Furthermore, the dual-allergen exposure hypothesis (or Lack hypothesis, authored by Gideon Lack¹⁷) in part suggests that epicutaneous allergen exposure in early life might promote allergic sensitization as the first step in the allergic march.

The aim of this review is to explore the theoretical basis and supporting evidence for the hypothesis that skin inflammation and/or epithelial barrier dysfunction might be critical in the development of allergic sensitization, food allergy, and allergic airways disease. Then, we consider the implications of this hypothesis on disease prevention. In particular, we describe previous and current studies testing the effect of skin-barrier improvement interventions on primary and secondary prevention of allergic disease. Further, we explore key issues pertinent to the design and interpretation of existing and future studies concerning the potential prevention of the atopic march.

Dual-Allergen Exposure Hypothesis

The dual-allergen exposure hypothesis, which could explain the increase in food allergy prevalence,¹⁷ posits that exposure to environmental food allergens can lead to induction of sensitization

and subsequent food allergy if early-life skin barrier function is poor or if there is skin inflammation, such as occurs with AD. However, early oral ingestion of food allergens can abrogate this risk by helping to promote immune tolerance to foods. This hypothesis has a number of important implications.

The first implication is that early oral exposure to food allergens could help promote immune tolerance. The Learning Early About Peanut (LEAP) trial showed that regular exposure to peanut allergen from 4 to 11 months of age in children at high risk of peanut allergy (due to severe eczema or egg allergy) resulted in an absolute decrease in the cumulative incidence of food allergy of 11.8% (13.7–1.9%).¹⁸ Although trials evaluating a similar strategy for other allergens, including egg,^{19–22} have not been as definitive, when the results from multiple studies are pooled together, there is evidence that early introduction of egg (at 4–6 months of age) is effective at lowering the risk of egg allergy.²³ In contrast, no consistent evidence exists for an effect of age of introduction to cow's milk on cow's milk allergy.²³ These protective effects of early food allergen exposure appear to be allergen specific; early introduction of one allergen does not prevent the development of allergy to other allergens. Effects on other allergic disease outcomes, including eczema, are not clear.²³

The second implication of the dual-allergen hypothesis, and the primary focus of this review, is that if the skin barrier can be improved and/or the inflammation of AD can be proactively prevented, then the incidence of food allergy and possibly other forms of allergic disease also might be decreased. This represents a substantial shift in thinking concerning the target organ for food allergy prevention. We will describe the evidence to support this hypothesis and the research that is currently underway in this field.

Can the Skin be the Site of Initiation of Sensitization and Subsequent Allergic Disease?

It has been hypothesized that sensitization to allergens can occur through damaged skin associated with AD, which then increases the risk of food allergy and other forms of allergic disease.¹ The skin is a very important barrier to the external environment; this barrier is initially more permeable (in infancy) and becomes more effective with increasing age.²⁴ The decreased barrier function of infants is, at least in part, due to low concentrations of ceramides in the stratum corneum, with ceramide concentration increasing in the weeks after birth.²⁵ Eczematous skin also is characterized by decreased ceramide levels.²⁶ Skin barrier is impaired in AD, even in asymptomatic skin.²⁶ Impaired skin barrier function in the first week of life is associated with an increased risk of AD by 12 months of age, even when the effect of family history and null mutations in the filaggrin (*FLG*) gene are taken into account.²⁷ Interestingly, increased transepidermal water loss can be detected at day 2 of life in infants who develop food allergy at 2 years of age.²⁸ Impaired skin barrier is associated with innate immune activation that results in dysregulated immune responses to innocuous environmental antigens, such as allergens and bacteria, and then to unwanted skin inflammation, leading to the development of allergic sensitization.¹³ These dysregulated immune responses in turn lead to further impairment of the barrier function and thereby establish a feedback cycle of ongoing inflammation and injury.²⁹

There are accumulating data supporting the concept that allergic sensitization can occur through an impaired skin barrier. Studies of mice have shown that epicutaneous disruption followed by ex-

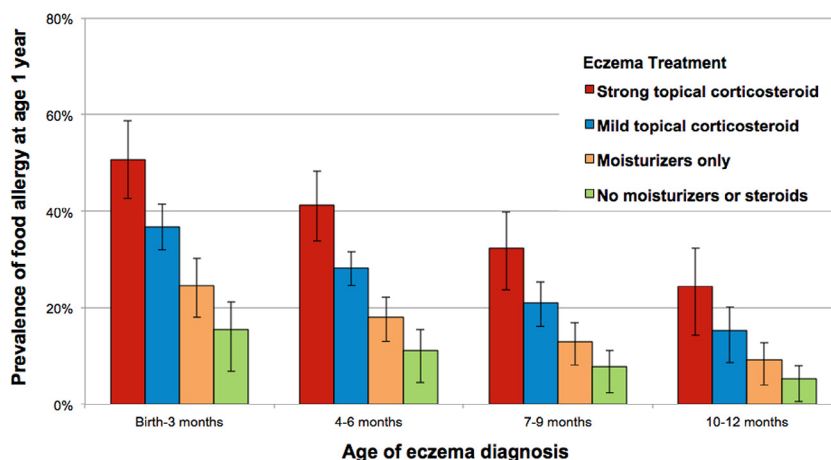


Figure 1. Infants with early-onset and more severe eczema are more likely to develop food allergy. Reproduced with permission from Martin et al.¹⁵

posure to egg and peanut allergens induces sensitization (increased specific immunoglobulin (Ig) E and IgG1).^{29,30} In a mouse model, repeated skin exposure to egg allergen was sufficient to induce not only AD-like skin lesions but also asthma-like airway hyper-responsiveness after exposure to egg aerosol.³⁰ Likewise, the use of topical creams that contain peanut oil for diaper rash has been associated with increased risk of peanut allergy.³¹ *FLG* null mutations, which impair skin-barrier function, increase risk of AD,³² food allergy,³³ and asthma.³² Collectively, this evidence suggests that initiation of the atopic march toward allergen sensitization and allergic disease could start with impaired skin-barrier function and AD.

Furthermore, environmental exposure to peanut allergens has been associated with increased risk of peanut sensitization and food allergy. The amount of peanut consumed within the home is associated with the level of peanut allergen in household dust and infant bedding.³⁴ Higher environmental peanut allergen levels are associated with increased risk of peanut sensitization and allergy in children with *FLG* null mutations³⁵ or AD,³⁶ but not in children without these risk factors. The heightened effect of environmental peanut allergen exposure on children with impaired skin-barrier function (due to *FLG* null mutations or AD) strongly suggests that sensitization to environmental allergens occurs through the skin.

There is evidence that AD increases the risk of new-onset food sensitization. Children with AD within the first 6 months of life without concurrent food sensitization had an increased risk of developing new-onset food and inhalant sensitization at 1 and 2 years of life.³⁷ However, it is noteworthy that most children developing food allergy do not have *FLG* mutations.³³

Recently, the influence of age at diagnosis and severity of AD on the development of allergic diseases has been explored.^{15,16} Infants with AD in the first year of life were at a marked increased risk of food allergy at 12 months.¹⁵ These associations were particularly strong in infants whose AD commenced within the first 3 months and who required topical steroids: 50.8% of these had challenge-proved food allergy¹⁵ (Fig 1). Furthermore, early-onset (<6 months) and persistent AD is most strongly associated with increased risk of asthma and rhinitis¹⁶ up to 18 years of age. These strong associations between early-onset and severe AD with other forms of allergic disease highlight the potential for preventive treatments to be effective if commenced in early life.

Current Evidence That Regular Application of Emollients Can Decrease the Incidence of AD

To date, 3 randomized trials have been published showing that regular application of emollients from the first weeks of life is as-

sociated with an approximate halving of the risk of development of AD^{38–40}; larger studies are underway (Table 1 presents a summary of trial methods and results). The published studies offer proof of concept that AD can be prevented using a skin-barrier improvement intervention (Fig 2). To date, all trials commenced treatment within the first weeks of life and continued to 6^{38,40} or 8³⁹ months of age. Two studies evaluated eczema prevalence at end of treatment; only 1 study⁴⁰ reported outcomes beyond the treatment period and demonstrated a promising but nonsignificant trend toward persistent decrease in the development of AD at 12 months of age, 6 months after the cessation of the treatment. Two studies^{38,39} used a standard emollient and the other used a lipid-rich ceramide-dominant formulation.⁴⁰ Although these initial trials support the use of emollient for AD prevention, it remains unclear whether long-lasting prevention of AD is achieved or whether the expression of AD is merely delayed or masked. Furthermore, emollient-only interventions have decreased occurrence of AD by 50%, leaving room for improvement, possibly by concurrent early proactive use of anti-inflammatory therapy to decrease non-lesional AD changes.

Could Regular Intervention to Improve Skin Barrier Also Result in a Lower Incidence of Food and Respiratory Allergy?

It remains unclear whether regular application of emollients to the skin of neonates might decrease the risk of sensitization to food allergens (Fig 2). Horimukai et al³⁹ did not observe a decrease in egg sensitization, but their study was not powered to detect an important decrease. Simpson et al³⁸ did not measure food sensitization. Our Prevention of AD By a Barrier Lipid Equilibrium Strategy (PEBBLES) study showed a trend for decreased food sensitization at 6 and 12 months of age but was not powered to detect important differences or measure true food allergy outcomes.⁴⁰ The short duration of follow-up in these studies has precluded examining asthma or allergic rhinitis outcomes. Importantly, prevention of food sensitization in the PEBBLES study was more effective when the lipid-rich emollient was introduced early (<2 weeks after birth) and used frequently (≥5 days per week).

Larger trials are currently underway to demonstrate the long-term effects of moisturizing on the incidence of AD beyond the treatment period and on the incidence of food allergy and allergic airways disease (Table 1). These include the large Norwegian Preventing Atopic Dermatitis and Allergies in Children (PREVENTADALL; N = 2,500), the UK Barrier Enhancement for AD Prevention (BEEP; N = 1,400),⁵⁹ and our PEBBLES (phase III; N = 760) trials. In the BEEP, parents reported food allergy and sensitization at 3 years of age, and these measures are being used to select infants for food

Table 1
Randomized Controlled Trials of Skin Barrier Interventions That Assess Effects on Allergic Disease Outcomes (in Addition to AD)

Study name (trial registration ID)	Sample size, country, population	Intervention	Outcome measures	Results or current progress
Completed studies				
Horimukai et al ³⁹ (UMIN000004544)	118 (59 vs 59), Japan, family history of AD	Daily 2e [Douhet] emulsion from first wk to 32 wk	Specific IgE to egg white and ovomucoid (≥ 35 kU _A /L)	No evidence of difference: egg white: 42% vs 45%, $P = .88$; ovomucoid: 19% vs 6.8%, $P = .17$
PEBBLES–phase II ⁴⁰ (ANZCTR12613000472774)	80 (41 vs 39), Australia, family history of allergic disease	Twice-daily EpiCeram from <3 wk to 6 mo	Sensitization to egg, peanut, or milk at 6 and 12 mo	Trend toward decreased food sensitization: 6 mo: 12.8% vs 22.9%, $P = .20$; 12 mo: 8.8% vs 19.4%, $P = .31$
Simpson et al ³⁸ (ISRCTN84854178)	124 (64 vs 60), UK and USA, family history of allergic disease	Daily application of 1 of 5 ^a emollients from within 3 wk to 6 mo	Not measured	—
Studies underway				
BEEP ⁵⁹ (ISRCTN21528841)	1,400, England, family history of allergic disease	Daily Double base Gel or Dipro base Cream for the first year of life	Food allergy diagnosis at 24 mo (combination of parent report, allergic sensitization, and food challenge); wheeze and allergic rhinitis at 12 to 24 mo	Results available in 2019
PEBBLES–phase III, (ACTRN12617001380381p)	760, Australia, family history of allergic disease	Twice-daily EpiCeram from <2 wk to 6 mo	Skin prick test to 3 food allergens at 12 mo followed by food challenge if wheal is ≥ 1 mm	Yet to commence recruitment; intended completion data in 2021
PREVENTADALL, (NCT02449850)	2,500, Norway, general population	Bath oil and Ceridal face cream ≥ 5 times/wk from 0.5 to 9 mo of age; factorial design with early food introduction as co-intervention	Skin prick test at 6 mo and then annually from 12 mo; food allergy at 12, 36, 48 mo and annually thereafter; asthma and allergic rhinitis	Commenced December 2014
Shimojo et al (UMIN00010838)	800, Japan, general population	Skin care and Synbiotics factorial design	Sensitization to food allergens at 9 mo and food allergy at 12 mo	Trial closed and analyses underway
PACI (UMIN000028043)	650, Japan, 7- to 13-wk-old infants with AD	Aggressive management of AD with topical anti-inflammatory medications	Challenge-proved IgE-mediated egg allergy at 28 wk	Commenced July 2017

Abbreviations: AD, atopic dermatitis; BEEP, Barrier Enhancement for AD Prevention (<https://www.nottingham.ac.uk/research/groups/cebd/projects/1eczema/beep-maintrial.aspx>); IgE, immunoglobulin E; PACI, Prevention of Allergy via Cutaneous Intervention (<http://paci-study.jp/english.html>); PEBBLES, Prevention of AD By a Barrier Lipid Equilibrium Strategy; PREVENTADALL, Preventing Atopic Dermatitis and ALLergies in Children (<https://clinicaltrials.gov/ct2/show/record/NCT02449850>).

^aParticipants could choose from sunflower seed oil, double-base gel, liquid paraffin in white paraffin, Cetaphil (Galderma Laboratories, Fort Worth, Texas) cream, or Aquaphor.

challenge. Measurement of food allergy at 3 years could miss cases of food allergy, because food sensitization⁴¹ and allergy^{42,43} peak at 12 months of age and decrease thereafter. In the PREVENTADALL, skin prick test and specific IgE will be measured at 6 and 12 months

and then annually thereafter; it is unclear whether food challenges will be performed. The PEBBLES will determine whether twice-daily application of EpiCeram (PuraCap Pharmaceuticals, Piscataway, New Jersey) for the first 6 months of life can decrease

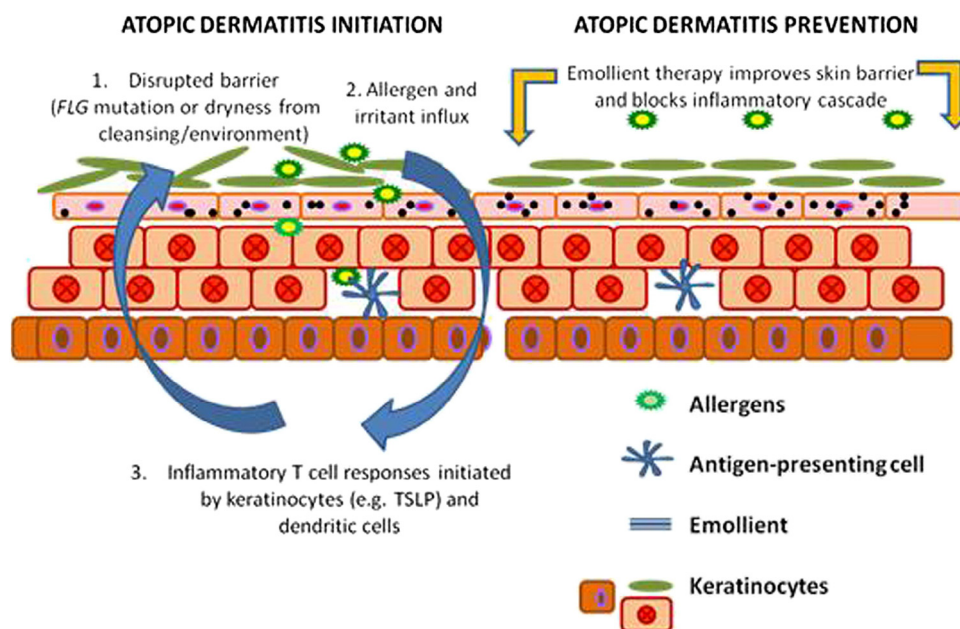


Figure 2. Skin barrier protection might prevent atopic dermatitis development. Reproduced with permission from Simpson et al.³⁸ *FLG*, filaggrin gene; TSLP, thymic stromal lymphopoietin.

the incidence of food allergy. In this study, food sensitization will be measured at 12 months and sensitized infants will be offered a food challenge using established protocols.⁴⁴ The methods used by these studies and their attendant issues are discussed below.

Key Issues in Studies of Trials That Evaluate the Impact of Emollients on Incidence of Food Allergy and Allergic Airways Disease

If we are to examine the effect of skin-barrier interventions in neonates, which group of infants should be assessed? Testing this form of intervention in a general population (all infants) can lead to population-based recommendations for neonatal skin care management that result in a lower risk of allergic disease. This approach has been adopted in the PREVENTADALL and a study by Shimojo et al (Table 1). Such studies also will allow us to test whether the intervention might have differential impact in populations with or without predisposition to developing allergic disease. Furthermore, because a large proportion of children affected by food allergy come from families without a family history,⁴⁵ such an approach could maximize the impact of this intervention within the community. However, this requires a large study sample; smaller samples are sufficient if only children at increased risk of allergic disease are recruited, because the baseline risk of allergic disease is higher,⁴⁵ making studies of high-risk infants more efficient.

If high-risk children are to be selected, then the issue arises of how to define “high risk.” Genetic polymorphisms (null mutations) in the *FLG* gene, which are carried by approximately 10% of the Caucasian population, result in impaired skin-barrier function and increase the risk of developing AD and asthma³² and food sensitization (with and without food allergy).³³ There is evidence that environmental exposures in early life increase the risk of developing AD in children with at least 1 *FLG* null mutation but does not influence risk in children without a mutation in this gene.^{35,46} As this form of intervention specifically aims to improve skin-barrier function and infants with *FLG* null mutations have innately poorer skin barrier, infants with such a mutation could gain particular benefit. However, identification of infants with *FLG* null mutations requires genetic screening, which is not feasible within the first weeks of life.

An alternative strategy is to recruit infants based on family history of allergic disease. This approach has been adopted by several studies (Table 1). A family history of allergic disease, particularly with at least 2 affected family members, modestly increases the risk that the infant will develop AD⁴ and food allergy.⁴⁵ Recruitment based on family history appears reasonable if there are restricted resources to conduct a study, particularly because a family history of allergic disease is easy to ascertain, but this is not always accurately reported. Nonetheless, population-based studies also are needed, as are studies that examine the impact of such interventions in individuals who have a *FLG* null mutation.

Primary vs Secondary Prevention

Secondary prevention includes the prevention of later allergic disease through better management of early signs of AD to restore skin-barrier function and decrease flares rather than the prevention of AD development before its onset. A secondary prevention approach to decrease the development of later allergic disease has been adopted by the recently registered Japanese Prevention of Allergy via Cutaneous Intervention (PACI) study (<http://paci-study.jp/english.html>), in which infants with AD 7 to 13 weeks old will be recruited and randomized to receive aggressive management to control symptoms of AD or standard treatment and tested for challenge-proved food allergy at 28 weeks of age. This approach avoids treating children who would not otherwise develop AD.

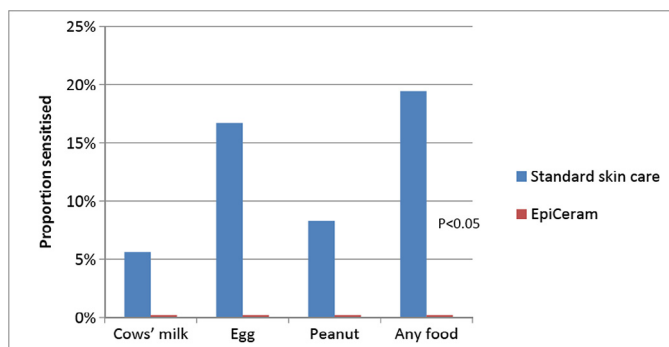


Figure 3. Effect of twice-daily EpiCeram vs standard skin care for the first 6 months on skin prick test reactivity to food allergens at 12 months. Results were limited to intervention participants who were treated at least 5 times per week on average. Reproduced with permission from Lowe et al.⁴⁰

However, there is evidence that the skin barrier is impaired for some time before the onset of AD symptoms in infants.²⁷ Although proactive treatment of subclinical disease after flares has been shown to decrease AD clinical recurrences,⁴⁷ there is no current known way to screen for subclinical disease before onset of AD symptoms. The period of impaired barrier function before onset of symptoms can allow for transcutaneous sensitization to environmental allergens and progression to the development of allergic disease.¹ In addition, even a brief period of eczema and impaired skin barrier could be sufficient to increase the risk of sensitization and allergic disease. Interventions that start once AD has commenced might have “missed the boat” for preventing these conditions. Recent studies using noninvasive techniques, such as transepidermal water loss measurement²⁷ or increased thymic stromal lymphopoietin by skin tape stripping,⁴⁸ have suggested that such techniques could be useful in identifying high-risk groups that would benefit from this intervention.

By contrast, for primary prevention studies, infants are treated before the onset of symptoms. Earlier initiation of treatment can increase the likelihood of efficacy because the infant skin barrier is relatively poor and improves with age. If the dual-allergen exposure hypothesis is correct, then induction of transepidermal sensitization is possible whenever the barrier is ineffective. In support of the importance of early initiation of treatment, in 1 trial published to date, infants who developed sensitization to foods at 12 months in the treated group commenced treatment later (mean 23 days, SD 2) than infants who did not develop food sensitization (mean 11.5, SD 5.7, $P = .04$).⁴⁰

Frequency of Emollient Treatment

It remains unclear how frequently emollient intervention is required to be effective. To date, studies have involved daily^{38,39} or twice-daily⁴⁰ application of prophylactic emollients. There are sparse data on the ideal frequency of application for different moisturizers required to best sustain barrier protection. Although frequent application would seem more likely to be effective, this needs to be weighed against decreased parental adherence. Increased application frequency increases treatment burden on caregivers and could limit adherence. Nevertheless, the PEBBLES study reported that no infant whose parents applied treatment on average for at least 5 days per week developed food sensitization (Fig 3).⁴⁰

Choice of Emollient

There are several products that could be used to build infant skin barrier with the aim of decreasing the incidence of AD and food

allergy. An array of products has been evaluated (Table 1). The key determinants of the suitability of an emollient for this purpose are (1) effectiveness in maintaining skin barrier, (2) safety, (3) acceptability, and (4) cost effectiveness.

Do various emollients have similar effectiveness?

At this time, there is insufficient evidence to allow comparison of the effectiveness of various emollients. If these studies can show an effect on allergic disease outcomes, then head-to-head trials might be required to establish relative emollient effectiveness. One trial⁴⁰ used a ceramide-dominant emollient formulated to have a physiologic ratio of ceramides, cholesterol, and fatty acids (3:1:1) rather than a standard emollient as the intervention because (1) it has been shown to accelerate the restoration of skin-barrier function, (2) it lessens severity of AD symptoms,⁴⁹ (3) AD-affected skin has low levels of ceramides,²⁶ and (4) it has a slightly acidic pH (5.0), which aids the production and secretion of ceramides by the skin.⁵⁰ There are increasing numbers of ceramide-dominant emollients entering the market, all of which are relatively expensive at this time and this could limit their use.

Safety

To date, the intervention creams used appear to be safe in this population. Safety of any topical barrier cream interventions for preventing disease in healthy infants is paramount. Infants are a particularly vulnerable population, and early-life exposures could have long-term consequences. Most treated infants would never develop AD or other forms of allergic disease, regardless of the intervention. Ongoing reporting of adverse reactions, including gastrointestinal adverse events and systemic events from the possibility of “mouthing” behavior at this age resulting in ingestion of the study cream, is required.

Addition of anti-inflammatory agents to topical barrier interventions has yet to be trialed as a preventive strategy. Although topical steroids are effective treatments for AD, and form the mainstay of routine care for children with moderate to severe AD, they have potential adverse effects with long-term or excessive use.⁵¹ Given the widespread “steroid phobia,” topical steroids are not likely to be suitable or acceptable for use in primary prevention in healthy infants. Similarly, no study has investigated the use of nonsteroidal creams, such as the calcineurin inhibitor pimecrolimus. Although largely refuted,⁵² the current requirement of the Food and Drug Administration for a “black box” label indicating a possible link between calcineurin inhibitors and lymphoma or skin cancer makes it unlikely that these would be acceptable to parents at this time for disease prevention (see Acceptability). New insights into mechanisms of AD will likely lead to safer and more effective anti-inflammatory approaches to control AD.

Acceptability

Acceptability of the intervention by parents is critical. This is an intervention that needs daily active participation by parents to be effective. If parents find the chosen intervention unacceptable because of ongoing concerns with safety, texture, smell, or appearance, it is unlikely that they will apply it frequently on their infant's skin. The use of multiple intervention creams, as adopted by Simpson et al³⁸ and the BEEP trial,⁵⁹ allows caregivers to select a treatment that is most acceptable to them and will help maximize adherence with the intervention. However, the issue with this approach is that each treatment might not have equivalent efficacy, and the overall study effect will be a weighted average of the effect of each treatment.

Cost effectiveness

Ultimately, the aim of this research is to provide a feasible means to prevent AD and allergic disease in future generations. These con-

Table 2

Causes of Skin Barrier Abnormalities

Genetic variants including filaggrin mutations
Immune activation, especially type 2 responses that decrease epithelial differentiation
Abnormalities in lipid synthesis and metabolism
Microbial dysbiosis, eg, <i>Staphylococcus aureus</i> colonization and decreased commensal staphylococci

ditions cause a substantial burden of illness and cost to families and the health care system. Interventions that lessen the burden of these conditions would be welcome, but if the cost of these interventions is prohibitively high, then it is unlikely they will be widely adopted. The costs of emollients vary dramatically; standard emollients are relatively cheap, whereas ceramide-dominant emollients are quite expensive. Compared with Aquaphor (Beiersdorf AG, Hamburg, Germany), an over-the-counter petroleum-based moisturizer, a ceramide-dominant emollient had a similar effect as a treatment of AD, but its higher cost made it less cost effective.⁵³

Alternate Strategies

Many approaches have been tried to prevent allergic diseases.^{11,12} Although controversy remains about the effects of many of these strategies, there is growing evidence that early introduction of allergenic foods during infancy provides allergen-specific protection against food allergy. If the dual-allergen exposure hypothesis¹⁷ is correct, then a combined strategy of early allergenic food exposure and barrier improvement strategies could be the optimal means to decrease the incidence of these conditions. At this time, there is currently insufficient evidence to recommend other strategies for allergic disease prevention. Interventions that have been trialed to date include the use of oral pre-⁵⁴ and pro-biotics⁵⁵ and hydrolyzed formulas.⁵⁶ There are ongoing trials to determine the effect of pre-⁵⁷ and postnatal⁵⁸ vitamin D supplementation. Although there is insufficient evidence to recommend the use of these strategies, in most cases there is a lack of robust study data to support their use rather than definitive evidence that they are not beneficial.

Conclusion

There is a strong link between early-life AD and allergic disease, which is theoretically causal in nature, through an impaired skin barrier and increased inflammatory responses. Emerging evidence suggests that interventions to improve skin-barrier function in neonates could decrease the incidence of eczema by approximately half, making it one of the most promising AD prevention strategies to date. Although the available data are not sufficient to make recommendations at this time, they offer an exciting prospect. Within the next 5 years, research will help determine whether the decrease in AD caused by regular emollient use during infancy also might lead to decreased food allergy and allergic airways disease. Beyond use of emollients to prevent dry skin and AD, more research is needed to identify the complex immune pathways, genetic abnormalities, lipid change, and microbial dysbiosis that contribute to food allergy sensitization in the skin necessary to develop new therapeutic approaches to prevent allergic disease (Table 2).⁶⁰

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