



The ins and outs of an 'outside-in' view of allergies: atopic dermatitis and allergy prevention

Marcus Shaker^{a,b,c}, Robert G.P. Murray^a, and Julianne A. Mann^{a,c,d}

Purpose of review

The skin barrier is a dynamic innate immune organ. This review summarizes the current understanding of how deficiencies associated with atopic dermatitis invite other atopic disorders of the allergic march.

Recent findings

Atopic dermatitis is characterized by skin barrier defects (such as mutations in filaggrin), intrinsic proallergic T-helper cell 2 immune dysregulation, and skin microbiome alterations. These factors promote the development of food allergy and asthma. Prevention of atopic dermatitis may involve topical emollients and oral probiotic supplementation, while some food allergies can be prevented by early introduction of potential food allergens to at-risk infants. Traditional therapies for atopic dermatitis involve skin hydration, emollients, and anti-inflammatory topical therapies including topical corticosteroids and calcineurin inhibitors. Dupilumab is a new and promising targeted biologic medication approved for use in adults with more severe atopic dermatitis; however, additional research is needed to determine whether this medication should be incorporated more broadly into management of severe childhood atopic dermatitis.

Summary

Atopic dermatitis management involves early diagnosis, skin barrier function support, mitigation of cutaneous inflammation, and concomitant risk stratification for the development of food allergy, asthma, allergic rhinitis, and environmental allergies.

Keywords

allergy prevention, atopic dermatitis, calcineurin inhibitors, dupilumab, early food introduction, filaggrin, food allergy, skin barrier, skin microbiome, transepidermal water loss

INTRODUCTION

Atopic dermatitis (also known as eczema) is a prevalent chronic skin condition thought to affect between 20 and 30% of infants [1]. The epithelium of patients with atopic dermatitis exhibits numerous abnormalities including skin matrix protein defects [2], decreased levels of antimicrobial peptides, and upregulation of T-helper cell 2-type cytokines [3,4]. These defects contribute to alterations of the skin microbiome [5]. Historically it was assumed that atopic dermatitis was the result of abnormal immunologic responses within the skin (the so-called inside out hypothesis), but in recent years the 'outside-in' hypothesis has gained traction [6–8]. The 'outside-in' paradigm describes defects in the skin barrier that allow penetration of microbes and passive transfer of protein allergens in susceptible infants, which in turn initiates a cycle of environmental sensitization and subsequent allergic disease [6].

THE MICROBIOME IN ATOPIC DERMATITIS

The role of the skin microbiome in the development of atopic dermatitis is currently a subject of intense investigation. *Staphylococcus aureus* may worsen skin barrier dysfunction through numerous mechanisms, including increased serine protease activity in keratinocytes [9^{***}]. An increased incidence of

^aChildren's Hospital at Dartmouth, ^bSection of Allergy and Clinical Immunology, Dartmouth-Hitchcock Medical Center, Lebanon, ^cGeisel School of Medicine at Dartmouth, Hanover, New Hampshire and ^dSection of Dermatology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA

Correspondence to Marcus Shaker, MD, MS, Section of Allergy and Clinical Immunology, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, USA. Tel: +1 603 653 9885; fax: +1 603 650 0907; e-mail: marcus.shaker@dartmouth.edu

Curr Opin Pediatr 2018, 30:000–000

DOI:10.1097/MOP.0000000000000646

KEY POINTS

- The allergy ‘outside-in’ paradigm highlights that the epithelium plays an important role in protecting against the development of allergic disease.
- Proactive emollient therapy may prevent or delay the development of atopic dermatitis.
- Early peanut introduction to at-risk infants with atopic dermatitis or egg allergy decreases the risk of subsequent peanut allergy.
- Dupilumab is the first biologic approved for management of refractory atopic dermatitis.

staphylococcus aureus colonization of the skin early in infancy predicts a higher risk of atopic dermatitis, and infants colonized with staphylococcus aureus tend to develop atopic dermatitis earlier than infants who are uncolonized [10²²,11]. Diversity of the skin microbiome is reduced in patients with atopic dermatitis as compared with healthy controls. Furthermore, among patients with atopic dermatitis, reduced diversity of the skin microbiome is associated with more severe clinical eczema phenotypes. Significantly, even nonlesional skin in patients with atopic dermatitis displays a less diverse microbiome from healthy controls, suggesting that patients with atopic dermatitis may have a globally impaired microbiome [12²²]. Treatment of atopic dermatitis with topical corticosteroids (with or without bleach baths) has been shown to restore microbial diversity in the skin so that it resembles nonlesional skin, although it still remains less diverse than the skin of controls [13].

Oral probiotics may have a role in treatment of atopic dermatitis, as suggested in a study of 50 children ages 4–17 showing that 12 weeks of daily supplementation with a probiotic containing *Bifidobacterium lactis*, *Bifidobacterium longum*, and *Lactobacillus casei* led to a statistically significant reduction in atopic dermatitis severity (as measured by the SCORAD index) as compared with controls [14²²]. Patients taking probiotics were also less likely to use topical corticosteroids for eczema flare treatment. Another recent study analyzed the fecal microbiome of children with atopic dermatitis with or without a concomitant food allergy. The authors identified a specific microbial signature in the group with food allergies, suggesting that, in children with atopic dermatitis, the gut microbiome differs between children with and without food allergy [15²²].

FILAGGRIN DEFECTS IN ASTHMA, ENVIRONMENTAL ALLERGY, AND FOOD ALLERGY

Defects in filaggrin (FLG), a skin matrix protein that promotes keratin aggregation, are strongly associated with atopic dermatitis. Experimentally, FLG deficiency has been shown to lead to a failure of the barrier function of the skin [16,17]. Physiologic FLG breakdown products also appear to play a role in maintaining the optimal pH of the skin, which in turn protects against adhesion of pathogens such as staphylococcus aureus.

Among patients with atopic dermatitis, those with FLG mutations are at increased risk for more severe and persistent skin disease [18], for environmental allergies [19], asthma [19], and food allergy [20,21²²]. Although FLG mutations are also strongly associated with peanut allergy [odds ratio (OR) 5.3, $P < 0.0001$] [20], it is also of interest that the use of peanut oil containing skin preparations increases the risk for peanut allergy [OR 6.8, 95% confidence interval (CI) 1.4–32.9] [22], apart from FLG abnormality. This suggests that the skin barrier may play a key role in immunologic priming and sensitization to this allergen.

THE EPITHELIUM, ATOPIC MARCH, AND ALLERGY PREVENTION

Children who initially develop atopic dermatitis are at higher risk for the subsequent development of food allergy, asthma, environmental allergies, and allergic rhinoconjunctivitis later in childhood (the so-called atopic march). Because atopic dermatitis is typically the first of these allergic diseases to present, it has been postulated that the skin may serve as the organ through which initial sensitization occurs [4]. In mouse model studies, mice whose skin was repeatedly exposed to egg allergen developed skin eczema, as well as asthma-like airway hyperreactivity after exposure to egg aerosol [23]. Worldwide, these allergic diseases are common during childhood, with asthma prevalence reported at 11.7–14.1%, rhinoconjunctivitis at 8.3–14.6%, and atopic dermatitis as high as 20–30% [1,24,25²²]. The prevalence of challenge-proven food allergy at 1 and 4 years of age is 11.0 and 3.8%, respectively [25²²].

The sequential trend in these conditions has led investigators to study the potential preventive effect of early atopic dermatitis treatments, resulting in several encouraging findings [26²²]. Because the majority of atopic dermatitis develops in the first 2 years of life [27], primary prevention efforts have focused on the prenatal period and early infancy. To

date, three studies have suggested that the application of emollients to the skin early in life may reduce the subsequent risk of developing atopic dermatitis [28,29,30[¶]]. In the Early Treatment of the Atopic Child study, treatment with cetirizine for 18 months decreased the odds of developing asthma in at-risk 1–2-year-old children with atopic dermatitis and environmental allergen sensitization over a 3-year follow-up (for those with house dust mite sensitization relative risk 1.6, 95% CI 1.3–1.9) [31].

Similar early preventive studies have looked at whether early food interventions can decrease the risk of developing food allergy. In the Learning Early from Peanut study, infants 4–11 months of age with severe eczema, egg allergy, or both were assigned early peanut consumption or avoidance. At 5 years of age the prevalence of peanut allergy was 1.9% in those who consumed peanut protein early vs. 13.7% in those who delayed introduction ($P < 0.001$) in the intention to treat population [32]. Subsequently, these same investigators instructed all participants to avoid peanuts for 12 months and then reassessed the durability of peanut tolerance, finding no significant loss of tolerance after 1 year of avoidance in previously tolerant at-risk children [33]. Given the success of early peanut introduction in peanut allergy prevention in high-risk infants (infants with severe eczema and/or egg allergy), these authors next evaluated exclusively standard-risk breast fed infants at 3 months of age, assigning them randomly to early introduction of six allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat) or to usual food introduction at 6 months of age. Although the intent to treat protocol analysis did not show significant differences in food allergies between groups, the per-protocol analysis demonstrated a lower food allergy prevalence in the early introduction group (2.4 vs. 7.3%, $P = 0.01$) [34].

Given the dramatic risk reduction in peanut allergy through early introduction in at-risk groups, recommendations have been issued around the globe encouraging early peanut protein introduction in select infants (infants with severe eczema and/or egg allergy). However, variation exists and international consensus is lacking. In the United States and Canada, a three step addendum guideline from the National Institute of Allergy and Infectious Diseases-sponsored expert panel was published in January 2017 [35^{¶¶}]. This guideline recommends infants with severe eczema and/or egg allergy undergo screening skin testing or serum IgE measurement before peanut is introduced in early infancy. In contrast the approaches endorsed by the Australasian Society for Clinical Immunology and Allergy (Australia/New Zealand) (ASCIA) and

the United Kingdom Department of Health (UKDOH) endorse early introduction of peanut butter without specific screening (ASCIA) or with a patient-preference sensitive approach to screening (UKDOH). It is notable that a no-screening approach was recently found to have superior health and economic outcomes in terms of the number of peanut allergy cases prevented, healthcare costs, and quality of life [36^{¶¶}]. In addition, a requirement for screening prior to peanut introduction may inadvertently delay early introduction, as only 31% of caregivers expressed willingness for screening procedures before 6 months of life [37^{¶¶}].

MANAGEMENT OF ATOPIC DERMATITIS

The presence of increased transepidermal water loss and skin barrier dysfunction in patients with atopic dermatitis explains why hydration and restoration of barrier function is so critical in management of atopic dermatitis [38]. Controversy has long existed as to the optimal bathing frequency; primary care physicians more often recommend infrequent bathing, whereas allergists and pediatric dermatologists more often recommend frequent bathing [39]. Although there are studies supporting both sides of this debate, those that support the benefits of frequent bathing are more numerous [40]. We advocate daily bathing, ideally a 20-min tub soak in plain warm (but not hot) water followed by application of topical corticosteroids to involved skin and a bland, thick emollient to normal skin within 3 min of exiting the bath before evaporative water losses occur [4,41]. For patients who do not have access to a bathtub, wet wraps can be an effective alternative [42[¶]]. Although emollients intended to more closely simulate the natural skin barrier have been designed [43], in one trial use of petrolatum emollients after skin hydration was as effective as using more expensive products [44]. We typically recommend plain Vaseline, which is highly effective when applied immediately after a tub soak. Once to twice weekly bleach baths are frequently recommended by dermatologists for patients with atopic dermatitis and a history of frequent staphylococcus infections, with the goal being to reduce the frequency of skin infections and subsequent exposure to oral antibiotics.

For moderate-to-severe eczema, the inflammation that results from this abnormal immune response is typically addressed through 1–2 week bursts of topical corticosteroid ointments of increasing but lowest necessary potency, at times with prophylactic twice-weekly topical corticosteroids to refractory or recurrent trouble spots [4]. Topical calcineurin inhibitors serve to reduce the T-cell

inflammatory response and can have benefits for children whose atopic dermatitis is insufficiently controlled with conventional topical corticosteroid therapy. The use of topical calcineurin inhibitors (considered a second-line agent approved for children at least 2 years of age) is a helpful addition for some patients, and many of our patients with more severe disease benefit from using these therapies preventatively 1–2 times daily Monday through Friday with topical steroids of lowest necessary potency on the weekends. Calcineurin inhibitors such as tacrolimus or pimecrolimus are beneficial in that they do not carry the risk of skin atrophy or suppression of the hypothalamic–pituitary axis. In 2006, the Food and Drug Administration placed a black box warning on tacrolimus ointment based on a theoretical risk of lymphoma and skin cancer arising from systemic use of calcineurin inhibitors among transplant recipients and in animal studies. Since then, numerous studies have failed to reveal a causal relationship with malignancy. In 2005 the American College of Allergy, Asthma, and Immunology (ACAAI), the American Academy of Allergy, Asthma, and Immunology (AAAAI), and the American Academy of Dermatology (AAD) concluded there was no evidence of increased incidence of lymphoma with short-term or intermittent long-term application of topical tacrolimus and pimecrolimus, despite use of these drugs in nearly 7 million persons [45,46]. In 2013 a subsequent report highlighted a 54-fold *decreased* risk in lymphoma incidence in topical pimecrolimus-exposed individuals compared with the US general population [47]. With the exception of those with Netherton syndrome, among patients with atopic dermatitis, serum concentrations resulting from topical application of tacrolimus are usually low or undetectable, and generally decrease over time as skin barrier function improves [48]. Topical calcineurin inhibitors are widely used by pediatric dermatologists and are generally felt to have a reassuring safety profile. Present recommendations from the AAAAI/ACAAI for the use of topical calcineurin inhibitors include: using these medications only as a second-line treatment, using only short courses of this medication, avoiding use in children less than 2 years of age and avoiding use in children with immunosuppression [45]. However, the AAD has noted that off-label use of calcineurin inhibitors may be appropriate for some patients with severe refractory atopic dermatitis because other alternative therapies in this subgroup (such as psoralen and ultraviolet A, and systemic immunosuppression with cyclosporine or azathioprine) carry known potential risks of malignancy and opportunistic infections. When used off-label, a discussion of risks and benefits of possible

therapies should be conducted in a patient-preference sensitive care model in which the perspectives of patients and families are elicited and incorporated into the decision process [46]. Indeed, a decision aid may be of some utility in refractory cases.

Newly approved crisaborole ointment, a nonsteroidal phosphodiesterase 4 inhibitor, has been shown to modestly reduce the severity of atopic dermatitis, although determining how this agent will be incorporated into treatment plans will require further study [49]. Crisaborole may be used to replace calcineurin inhibitors as Monday through Friday maintenance therapy for some severely affected patients.

Traditionally, severe refractory cases of atopic dermatitis may necessitate phototherapy and/or immunomodulatory or immunosuppressive therapy including agents such as methotrexate, cyclosporine, azathioprine, and mycophenolate mofetil, in addition to topical therapy [4]. The first biologic designed to treat atopic dermatitis, dupilumab, was approved in early 2017 as a very effective inhibitor of the IL-4 and IL-13 pathways. In randomized, double-blind, placebo-controlled trials of adults with moderate-to-severe atopic dermatitis despite regular treatment with topical corticosteroid and calcineurin inhibitor use, dupilumab was evaluated in 4–12 weeks trials. Rapid and dose dependent improvements were noted. A 50% reduction in the Eczema Area and Severity Index score occurred in 85% of treated patients compared with 35% of placebo recipients ($P < 0.001$) [50]. Although not approved as an asthma treatment yet, evidence suggests that dupilumab may also be effective for this condition as well [51,52].

CONCLUSION

It is now clear that early onset severe atopic dermatitis is a red flag that should suggest not only the need for early evaluation and treatment of the skin condition, but also risk-stratification for food allergy, asthma, and inhalant allergies. A partnership between primary care, pediatric allergy, and dermatology specialists is essential to effectively manage this chronic condition. Optimal management may in turn have the potential to prevent the development of food allergy and possibly other allergic diseases.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

M.S. has a family member who is CEO of Altrix Medical.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Martin PE, Koplin JJ, Eckert JK, *et al.* The prevalence and socio-demographic risk factors of clinical eczema in infancy: a population-based observational study. *Clin Exp Allergy* 2013; 43:642–651.
2. Palmer CN, Irvine AD, Terron-Kwiatkowski A, *et al.* Common loss-of-function variants of epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; 38:4441–4446.
3. Boguniewicz M, Leung DY. Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. *Immunol Rev* 2011; 242:233–246.
4. Schneider L, Tilles S, Lio P, *et al.* Atopic dermatitis: a practice parameter update. *J Allergy Clin Immunol* 2013; 131:295–299.
5. Mijalovic H, Fallon PG, Irvine AD, *et al.* Effect of filaggrin breakdown products on growth of and protein expression by *Staphylococcus aureus*. *J Allergy Clin Immunol* 2011; 126:1184.
6. Irvine AD, McLean WHI, Leung DY. Filaggrin mutations associated with skin and allergic disease. *NEJM* 2011; 365:14.
7. Elias PM, Hatano Y, Williams ML. Basis for barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. *J Allergy Clin Immunol* 2008; 121:1337–1343.
8. Lack G. Update on risk factors for food allergy. *J Allergy Clin Immunol* 2012; 129:1187–1195.
9. Williams MR, Nakatsuji T, Stanford JA, *et al.* *Staphylococcus aureus* induces increased serine protease activity in keratinocytes. *J Invest Dermatol* 2017; 137:377–384.

Skin colonization with *Staphylococcus aureus* may worsen skin barrier dysfunction through numerous mechanisms, including increased serine protease activity in keratinocytes.

10. Meylan P, Lang C, Mermoud S, *et al.* Skin colonization by *Staphylococcus aureus* precedes the clinical diagnosis of atopic dermatitis in infancy. *J Invest Dermatol* 2017; 137:2497–2504.

Infants colonized with *Staphylococcus aureus* tend to develop atopic dermatitis earlier than infants who are uncolonized.

11. Totte JE, Van der Felz WT, Hennekam M, *et al.* Prevalence and odds of *Staphylococcus aureus* carriage in atopic dermatitis: a systematic review and meta-analysis. *Br J Dermatol* 2016; 175:687–695.
12. Clausen ML, Agner T, Lilje B, *et al.* Association of disease severity with skin microbiome and filaggrin gene mutations in adult atopic dermatitis. *JAMA Dermatol* 2018; 154:293–300.

Among patients with atopic dermatitis, reduced diversity of the skin microbiome is associated with more severe clinical eczema phenotypes. Significantly, even nonlesional skin in patients with atopic dermatitis displayed a less diverse microbiome from healthy controls, suggesting that patients with atopic dermatitis may have a globally impaired microbiome.

13. Gonzalez ME, Schaeffer JV, Orlow SJ, *et al.* Cutaneous microbiome effects of fluticasone propionate cream and adjunctive bleach baths in childhood atopic dermatitis. *J Am Acad Dermatol* 2016; 75:481–493.
14. Navarro-Lopez V, Ramirez-Bosca A, Ramon-Vidal D, *et al.* Effect of oral administration of a mixture of probiotic strains on SCORAD index and use of topical steroids in young patients with moderate atopic dermatitis. *JAMA Dermatol* 2018; 154:37–43.

Supplementation with a probiotic containing *Bifidobacterium lactis*, *Bifidobacterium longum*, and *Lactobacillus casei* led to a statistically significant reduction in atopic dermatitis severity (as measured by the SCORAD index) as compared with controls.

15. Fieten KB, Totte JEE, Levin E, *et al.* Fecal microbiome and food allergy in pediatric atopic dermatitis: a cross-sectional pilot study. *Int Arch Allergy Immunol* 2018; 175:77–84.

In children with atopic dermatitis, the gut microbiome differs in children with and without food allergy.

16. Mildner M, Eckhard J, Kezic S, *et al.* Knockdown of filaggrin impairs diffusion barrier function and increases UV sensitivity in a human skin model. *J Invest Dermatol* 2010; 130:2286–2294.
17. Gruber R, Elias PM, Crumrine D, *et al.* Filaggrin genotype in ichthyosis vulgaris predicts abnormalities in epidermal structure and function. *Am J Pathol* 2011; 178:2252–2263.
18. Henderson J, Northstone K, Lee SP, *et al.* The burden of disease associated with filaggrin mutations: a population-based longitudinal birth cohort study. *J Allergy Clin Immunol* 2008; 12:872.

19. Bonnelykke K, Phipps CB, Tavendale R, *et al.* Filaggrin gene variants and atopic disease in early childhood assessed longitudinally from birth. *Pediatr Allergy Immunol* 2010; 21:954–961.
20. Brown SJ, Asai Y, Cordell HJ, *et al.* Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. *J Allergy Clin Immunol* 2011; 127:661–667.
21. Kono M, Akiyama M, Inoue Y, *et al.* Filaggrin gene mutations may influence the persistence of food allergies in Japanese primary school children. *Br J Dermatol* 2018; doi: 10.1111/bjd.16375. [Epub ahead of print]

Filaggrin mutations confer a higher risk of persistent food allergies. Children with filaggrin mutations tend to have food allergies that persist into later childhood and beyond, whereas infants and toddlers without filaggrin mutations are more likely to outgrow their food allergies.

22. Lack G, Fox D, Northstone K. Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 2003; 348:977–985.
23. Spergel JM, Mizoquchi E, Brewer JP, *et al.* Epicutaneous sensitization with protein antigen induces localized allergic dermatitis and hyperresponsiveness to methacholine after single exposure to aerosolized antigen in mice. *J Clin Invest* 1998; 101:1614–1622.
24. Mallol J, Crane J, von Mutius E, *et al.* The international study of asthma and allergies in childhood (ISAAC) phase three: a global synthesis. *Allergol Immunopathol* 2013; 41:73–85. Shaw TE, Currie GP, Koudelka CW, *et al.* Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol* 2011; 131(1): 77.
25. Peters RL, Koplin J, Gurrin L, *et al.* The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: Healthnuts age 4 year follow-up. *J Allergy Clin Immunol* 2017; 140: 145–53.e8.

In this Australian population-based cohort of 5276 children enrolled at 1 year of age, the prevalence of food allergy at 1 and 4 years of age was 11.0 and 3.8%.

26. Lowe AJ, Leung DYM, Tang MLK, *et al.* The skin as a target for prevention of atopic dermatitis. *Ann Allergy Asthma Immunol* 2018; 129:145–151.

The review summarizes evidence that both barrier dysregulation and skin inflammation in atopic dermatitis may actually serve as a precursor to the subsequent development of food allergy and asthma.

27. Quille-Roussel C, Raynaud F, Saurat JH. A prospective computerized study of 500 cases of atopic dermatitis in childhood: initial analysis of 250 parameters. *Acta Derm Venereol Suppl* 1985; 114:87–92.
28. Horimukai K, Morita K, Narita M, *et al.* Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol* 2014; 134:824–830.
29. Simpson EL, Chalmers JR, Hanifin JM. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Immunol* 2014; 134:818–823.
30. Lowe AJ, Su JC, Allen KJ, *et al.* A randomized trial of a barrier lipid replacement strategy for the prevention of atopic dermatitis and allergic sensitization: the PEBBLES pilot study. *Br J Dermatol* 2018; 178:e19–e21.

The study found a trend toward decreased food sensitization at 6 and 12 months of age which was more effective when emollients were introduced at less than 2 weeks after birth and used on at least 5 days a week.

31. Warner JO. A double-blind, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months' treatment and 18 months' posttreatment follow-up. *J Allergy Clin Immunol* 2001; 108:929–937.
32. DuToit G, Roberts G, Sayre PH, *et al.* Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015; 373:803–813.
33. DuToit G, Sayre PH, Roberts G, *et al.* Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med* 2016; 374:1435–1443.
34. Perkin M, Logan K, Tseng A, *et al.* Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med* 2016; 374:1733–1743.
35. Togias A, Cooper S, Acebal M, *et al.* Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious-Diseases sponsored expert panel. *J Allergy Clin Immunol* 2017; 139:29–44.

These guidelines present a risk stratification approach for early peanut introduction in infants.

36. Shaker M, Stukus D, Chan ES, *et al.* To screen or not to screen': comparing the health and economic benefits of early peanut introduction strategies in five countries. *Allergy* 2018; doi:10.1111/e11.13446. [Epub ahead of print]

In this economic analysis of early peanut introduction strategies, a no-screening approach was found to have superior health and economic outcomes in terms of the number of peanut allergy cases prevented, healthcare costs, and quality of life.

37. Greenhawt M, Chan ES, Fleisher DM, *et al.* Caregiver and expecting caregiver support for early peanut introduction guidelines. *Ann Allergy Asthma Immunol* 2018; pii: S1081-1206 (18) 30161-3. doi: 10.1016/j.anaai.2018.02001. [Epub ahead of print]

In this survey of caregivers and expecting caregivers, 54% felt timing of food introduction was important but only 31% were willing to have screening procedures before 6 months of age.

38. Kelleher M, Dunn Galvin A, Hourihane JO, *et al.* Skin barrier dysfunction measured by transepidermal water loss at 2 days and 2 months predates and predicts atopic dermatitis at 1 year. *J Allergy Clin Immunol* 2015; 135: 930–935.

39. Cardona ID, Kempe E, Hatzenbeuhler JR, *et al.* Bathing frequency recommendations for children with atopic dermatitis: results of three observational pilot surveys. *Pediatr Dermatol* 2015; 32:e194–e196.
40. Cardona ID, Stillman L, Jain N. Does bathing frequency matter in pediatric atopic dermatitis? *Ann allergy Asthma Immunol* 2016; 117:9–13.
41. Hajar T, Hanifin JM, Tofte SJ, *et al.* Prehydration is effective for rapid control of recalcitrant atopic dermatitis. *Dermatitis* 2014; 25:56–59.
42. Cooper CA, DeKlotz CMC. Warming to the idea of wet wraps. *Pediatr Dermatol* 2017; 34:737–738.
- For patients who do not have access to a bathtub, wet wraps can be an effective alternative for skin hydration.
43. Sajic D, Asiniwasis R, Skotnicki-Grant S. A look at epidermal barrier function in atopic dermatitis: physiologic lipid replacement and the role of ceramides. *Skin Therapy Lett* 2012; 16:6–9.
44. Miller DW, Koch SB, Yentzer BA, *et al.* An over the counter moisturizer is as clinically effective as, and more cost-effective than, prescription barrier creams in the treatment of children with mild-to-moderate atopic dermatitis: a randomized controlled trial. *J Drugs Dermatol* 2011; 10:531–537.
45. Fonacier L, Spergel J, Charlesworth E, *et al.* Report of the topical calcineurin inhibitor task force of the American College of Allergy, Asthma, and Immunology and the American Academy of Allergy, Asthma, and Immunology. *J Allergy Clin Immunol* 2005; 115:1249–1253.
46. Berger TG, Duvic M, Van Voorhees AS, *et al.* The use of topical calcineurin inhibitors in dermatology: safety concerns. Report of the American Academy of Dermatology Association Task Force. *J Am Acad Dermatol* 2006; 54:818–823.
47. Carr W. Topical calcineurin inhibitors for atopic dermatitis. Review and treatment recommendations. *Paediatr Drugs* 2013; 15:303–310.
48. Rustin MH. The safety of tacrolimus ointment for the treatment of atopic dermatitis: a review. *Br J Dermatol* 2007; 157:861–873.
49. Paller AS, Tom WL, Lebwohl MG, *et al.* Efficacy and safety of crisaborole ointment, a novel nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol* 2016; 75:494–503.e6.
50. Beck LA, Thaci D, Hamilton JD, *et al.* Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med* 2014; 371:130–139.
51. Wenzel S, Corren J, Maspero J, *et al.* Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high dose inhaled corticosteroids plus a long acting beta-2 agonist: a randomized double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet* 2016; 388:31–44.
52. Wenzel S, Ford L, Pearlman D, *et al.* Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013; 368:2455–2466.