

New Treatment Paradigms in Atopic Dermatitis: Understanding and Incorporating Recent and Emerging Therapies



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Introduction

Update on Epidemiology, Diagnosis, and Disease Course of Atopic Dermatitis

Review of Critical Issues in the Pathogenesis of Atopic Dermatitis

Assessing the New and Emerging Treatments for Atopic Dermatitis

The Changing Paradigm of Atopic Dermatitis Therapy

Post-Test and Evaluation Form

Original Release Date: **June 2016**

Most Recent Review Date: **June 2016**

Expiration Date: **May 31, 2018**

Estimated Time to Complete Activity: **2.0 hours**

Jointly provided by



Global Academy for
Medical Education



SKIN DISEASE
EDUCATION
FOUNDATION

Supported by an educational grant from
Anacor Pharmaceuticals, Inc.

Reprinted from
*Seminars in Cutaneous
Medicine and Surgery*

The manuscript was originally
published as a supplement to *Seminars
in Cutaneous Medicine and Surgery*,
Vol. 35, No. 5S, June 2016.

It has been reviewed and approved
by the faculty as well as the Editors
of *Seminars in Cutaneous Medicine
and Surgery*.

The Faculty acknowledge the editorial
assistance of Global Academy
for Medical Education, LLC, and
Joanne Still, medical writer, in the
development of this supplement.

This continuing medical education
(CME/CE) supplement was developed
from a closed-session roundtable
held during Skin Disease Education
Foundation's 40th Hawaii Dermatology
Seminar, February 17, 2016 in
Waikoloa, Hawaii. Neither the editors
of *Dermatology News* nor the Editorial
Advisory Board nor the reporting staff
contributed to its content. The opinions
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Target Audience

This journal supplement is intended for dermatologists, dermatology residents, internists, primary care physicians, nurse practitioners, physician assistants, and other clinicians who treat patients with skin diseases.

Educational Needs

Atopic dermatitis (AD), also called eczema, is a chronic, relapsing inflammatory skin disease that is associated with significant morbidity and costs to patients and their families. AD occurs most often in infants and children, and its onset decreases substantially with age. Approximately 80% of children with atopic dermatitis develop asthma or allergic rhinitis later in childhood. Recent research into the pathophysiology of AD indicates that it has a complex etiology involving multiple immunologic and inflammatory pathways and environmental triggers, as well as mutations in the *filaggrin* gene in many—but not all—patients.

Because AD has no cure, disease management is directed toward symptom relief, patient/parent education, and the prevention of secondary complications.

Clinicians need to remain up-to-date on the benefits and risks of all treatment options available as well as make the appropriate selection for their patients. Traditional AD treatments—including topical corticosteroids and topical calcineurin inhibitors—are likely to continue to be important in the management of AD. With the increasing understanding of the role of epidermal skin barrier defects in AD pathogenesis, the importance of moisturization beginning early in life has achieved new prominence. In addition, there is renewed interest in dilute bleach baths as a means of controlling *Staphylococcus aureus* colonization in selected patients. Evidence shows that this method is both anti-inflammatory and anti-infective. Continuing research will provide insights regarding the optimization of these familiar strategies.

In addition, research that has provided new insights into the pathogenesis of AD has led to the development of new and emerging therapies. Phase III clinical trials have been completed on two new agents, in particular—crisaborole, a boron-based small molecule that inhibits phosphodiesterase-4, and dupilumab, a monoclonal antibody that targets the interleukin-4/interleukin 13 receptor α chain.

Clinicians must remain informed about newer strategies and new and emerging therapeutic agents with novel mechanisms of action. Expert reviews of the recent literature are necessary to discuss important research findings and to provide perspective regarding how these findings should affect clinical practice.

Learning Objectives

By reading and studying this supplement, participants should be better able to:

- Discuss the most recent information on the epidemiology and pathogenesis of AD, and how this is likely to affect the management of patients with AD.
- Explain how the current and emerging understanding of *filaggrin* loss-of-function mutations affect the development of AD.
- Recognize the rationale for and mechanisms of action of existing and emerging therapies for AD.
- Analyze how existing and emerging therapies fit into the AD treatment paradigm.
- More effectively individualize patient treatment strategies by considering the full range of current and emerging therapeutic options.

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Staff and Advisory Board Disclosures: The CME & PD staff and Advisory Board have nothing to disclose.

CME Reviewer: Cindy England Owen, MD, Assistant Professor, Division of Dermatology, University of Louisville School of Medicine, has no relevant financial relationships to disclose.

Global Academy for Medical Education Staff: Sylvia H. Reitman, MBA, DipEd; Jenny Campano; and Joanne Still, BA, have no relevant financial relationships to disclose.

Off-Label/Investigational Use Disclosure

This CME/CE activity discusses the off-label use of certain approved medications as well as data from clinical trials on investigational agents. Any such material is identified within the text of the articles.

This continuing medical education (CME/CE) supplement was developed from a closed-session roundtable held at the Skin Disease Education Foundation's 40th Annual Hawaii Dermatology Seminar, February 17, 2016, in Waikoloa, Hawaii. The Guest Editors acknowledge the editorial assistance of Global Academy for Medical Education and Joanne Still, medical writer, in the development of this supplement. The manuscript was reviewed and approved by the Guest Editors as well as the Editors of *Seminars in Cutaneous Medicine and Surgery*. The ideas and opinions expressed in this supplement are those of the Guest Editors and do not necessarily reflect the views of the supporter, Global Academy for Medical Education, the University of Louisville, or the Publisher.

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Introduction

Numerous epidemiologic and clinical studies within the past decade have demonstrated that genetic, environmental, and immunologic factors all affect atopic dermatitis (AD) development as well as its clinical picture, degree of severity, and course. In addition to the classic predictors of AD development such as family history and urban environment, elevated transepidermal water loss in newborns has been found to be a strong predictor of AD, regardless of filaggrin (*FLG*) gene status. In addition, recently recognized predictors of disease course and severity include onset of AD signs and symptoms before 12 months of age and the presence of *FLG* gene mutations and concomitant immunoglobulin E sensitization early in life.

The complex interactions between *FLG* gene defects and the environment continue to be a topic of great interest in the quest to better understand the pathologic pathways in AD, including the initiation, maintenance, and promotion of this disease.

The result of research in the past decade has been the development of new and emerging clinical and pharmacologic strategies for early identification and intervention in AD and other atopic diseases. These treatments focus on the blockade of inflammatory cytokines, especially those that derive from T helper cell type 2. Among the proinflammatory cytokines that have been identified as promising therapeutic targets are phosphodiesterase-4 and the interleukin-4/interleukin-13 receptor α chain. Two agents that have been developed that address these two cytokines are crisaborole and dupilumab, respectively. Both of these agents have been studied in phase III clinical trials, and publication of the results of those studies is expected in the near future.

The articles in this supplement provide updated information on the epidemiology, pathogenesis, diagnosis, and disease course of AD, as well as the new and emerging treatments.

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Publication of this CME/CE article was jointly provided by University of Louisville and Global Academy for Medical Education, LLC, and is supported by an educational grant from Anacor Pharmaceuticals, Inc.

Dr Eichenfield has received an honorarium for his participation in this activity. He acknowledges the editorial assistance of Joanne Still, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal article.

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Update on Epidemiology, Diagnosis, and Disease Course of Atopic Dermatitis

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Abstract

Studies of the prevalence of atopic dermatitis (AD) have provided insights into associated environmental risk factors, demonstrating the complex interactions between the presence of filaggrin (*FLG*) gene defects and environment. Among other important findings is that elevated transepidermal water loss (TEWL) in newborns is a strong predictor of AD, regardless of *FLG* status. Recently recognized predictors of disease course and severity include onset of AD signs and symptoms before 12 months of age and the presence of an *FLG* mutation and concomitant immunoglobulin E sensitization early in life.

Semin Cutan Med Surg 35(supp5):S84-S88

© 2016 published by Frontline Medical Communications

Keywords

Atopic dermatitis; eczema; filaggrin; food allergy; peanut allergy; obesity; skin infection

Within the past 5 to 10 years, the results of research regarding the epidemiology, diagnosis, and course of atopic dermatitis (AD) have led to new insights in understanding this disease. In turn, these new insights have provided the necessary background for developing novel prevention and management strategies.

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Publication of this CME/CE article was jointly provided by University of Louisville and Global Academy for Medical Education, LLC, and is supported by an educational grant from Anacor Pharmaceuticals, Inc.

Dr Simpson has received an honorarium for his participation in this activity. He acknowledges the editorial assistance of Joanne Still, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal article.

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Environmental Risk Factors for AD—Insights From Disease Prevalence Studies

AD is estimated to affect between 15% and 20% of children in developed countries.¹ The evidence on adult AD prevalence is less robust, with estimates ranging from 1% to 10%, depending on how AD is defined in the various studies considered. Pediatric AD prevalence appears to be increasing in developing countries, with a maximum prevalence of 20% to 30% in some populations.² The reasons for the increasing prevalence of pediatric AD are unclear, but large-scale studies suggest that several environmental factors may be responsible.

The first systematic, international investigation of AD prevalence from regions outside of Northern Europe came from the International Study of Asthma and Allergies in Childhood (ISAAC) in 1999.³ In ISAAC, Williams and colleagues noted wide variations in AD symptom prevalence between and within countries with similar ethnic groups, an observation that led the authors to suggest that disease expression might depend largely on environmental factors.³

The Urban/Rural Gradient

A number of studies from various countries and regions have noted the increase in AD among populations worldwide, and regional studies have suggested and supported the notion of an urban/rural gradient in AD disease prevalence. Schram and colleagues⁴ performed a systematic analysis of 26 of these studies to determine whether an urban/rural gradient could be established, and concluded that “there is some evidence” of a higher risk for AD in urban versus rural regions.

More recently, Wang et al⁵ noted that the increase in AD among Taiwanese infants overall increased from 6.7% in 2005 to 7.9% in 2007; in Taipei, the 40th most populous urban area in the world, the prevalence of AD among 6- to 7-year-old children significantly increased over a period of about 13 years, from 23.9% in 1994, to 26.3% in 2002, and to 29.8% in 2007. These authors observed that genetic variability in the population could not have changed within this time frame and proposed that “environmental factors are likely to be responsible for the rise” in AD prevalence.

In another example, a cross-sectional study of preschool children from Shanghai, China, showed an overall AD prevalence of 8.3%, with a significantly higher prevalence in the core urban area (10.2%) than in the regions farthest from the urban area (4.6%).⁶

The specific factors that may explain these increases in AD prevalence, as well as the differences between prevalence in urban and rural areas, have not yet been established. Some studies suggest that exposure to microbes found in agricultural environments protect the developing immune system from T helper cell type 2 (T_H2) overactivity.^{7,8} McFadden and colleagues⁹ argue that early life low-dose chemical exposures via epithelial and epidermal surfaces promote T_H2 responses.

Thyssen and colleagues¹⁰ suggest a lack of ultraviolet (UV) radiation exposure may be an additional factor contributing to the rise in AD prevalence, given the beneficial effect of UV radiation on epidermal functioning and inflammation.

More recently, Kathuria and Silverberg¹¹ studied the correlation between small-particle air pollution, climate, and childhood eczema in a US population database of children 17 years of age and younger. The investigators considered measurements of air pollutants and ozone levels from the 2006-2007 US Environmental Protection Agency report and measurements of humidity, ultraviolet radiation index, outdoor air temperatures, and precipitation levels from the National Climatic Data Center. These investigators found a number of statistical associations between these various factors and AD, but further study is required to verify and further characterize these findings.

Interactions Between Genetics and Environment

Patients who carry a filaggrin loss-of-function (*FLG* null) mutation have been shown to have a greater than threefold increased risk for developing AD,^{12,13} and both rare and common *FLG* null mutations of various types have been identified in patients with AD worldwide. *FLG* mutations cause a loss of *FLG* protein of at least 50%, leading to multiple biophysical defections in skin barrier function, including elevated pH, a disorganized stratum corneum, reduced lipid content, and increased transepidermal water loss (TEWL).¹⁴

However, not all children with an *FLG* defect develop AD, and cohort studies are beginning to elucidate the complex interactions between environment and *FLG* status. For example, cat ownership enhances the detrimental effects of *FLG* mutations, whereas dog ownership may be protective.^{15,16} Another cohort study confirmed the importance of *FLG* in predicting AD, but showed skin barrier dysfunction early in life (that

is, elevated TEWL at 2 days and 2 months of age) was the strongest predictor of AD development, independent of *FLG* status.¹⁷ These data suggest environmental factors affecting the skin barrier, together with a person's genetic profile, help determine the risk for developing AD. A similar study in a cohort of Japanese infants also demonstrated that early TEWL is a strong and independent predictor of AD.¹⁸

Disease Presentation

Morphology

Morphologically, AD presents with the classic signs of erythema, papulation, lichenification, excoriation, oozing, and crusting. This classic presentation can vary in patients with skin of color. For example, in darker skin types, lichenification can resemble flat-topped lichenoid papules, and follicular accentuation and hyper- and hypopigmentation are common. In addition, a grayish-white discoloration (sometimes referred to as “ashy” skin) is a manifestation of xerosis and, possibly, ichthyosis vulgaris.

AD Configuration

In the classic configuration, AD presents as poorly demarcated papules and plaques; however, AD also may have a well-demarcated nummular configuration, resembling nummular dermatitis. True nummular dermatitis, unrelated to atopic disease, is uncommon in children.¹⁹

Age-Specific AD Distribution Patterns

In children, AD usually begins in the face, moves to the extensors, and becomes more accentuated over time in the antecubital and popliteal fossae (**Figure**). In adults, the face is commonly involved, and periocular disease is common. It is unclear at this time whether different patterns of distribution reflect differences in pathophysiology or prognosis, and/or whether different patterns warrant a different therapeutic approach.

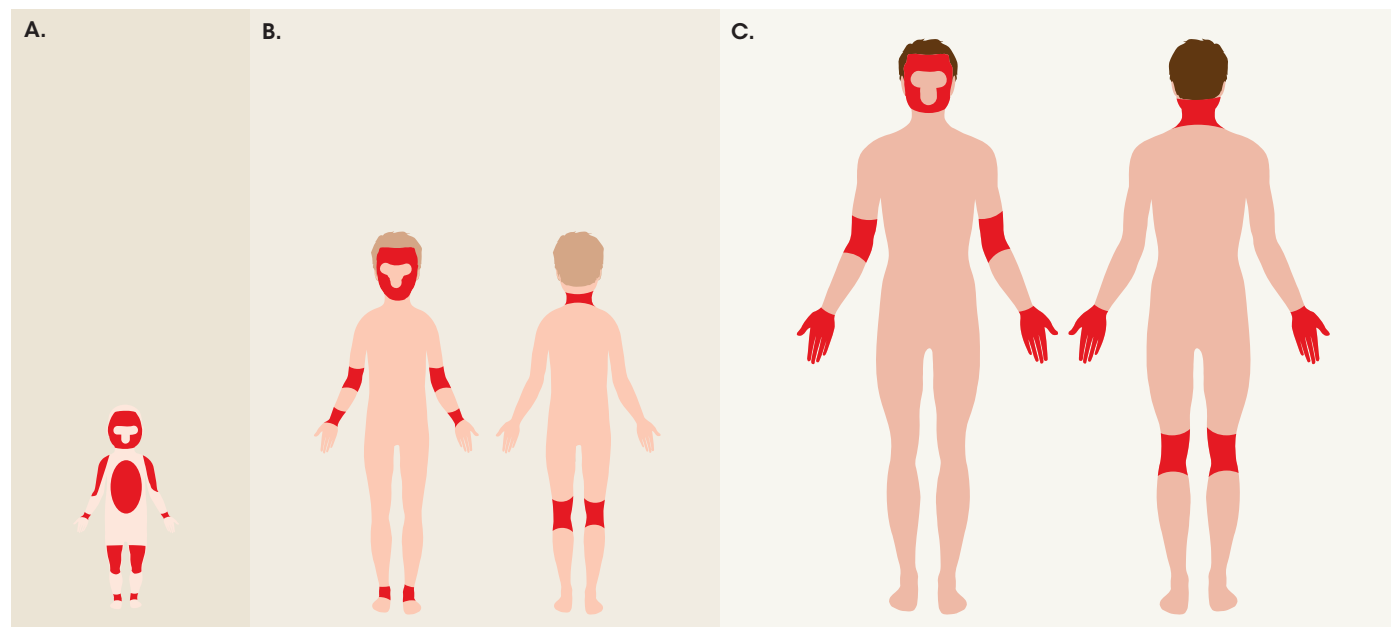


FIGURE Atopic Dermatitis: Age-Related Patterns of Involvement.

A. In babies less than 2 years of age, the signs of atopic dermatitis (AD) first appear on the scalp, forehead, and face (typically, the cheeks), then on the extensor surfaces of the extremities. **B.** In older children, AD is more accentuated in the flexural folds: the nape of the neck, the antecubital popliteal fossae, and the wrists and ankles. **C.** In adults, the pattern of distribution commonly includes the face, often with periocular involvement, the hands, and the flexural areas of the neck, arms, and legs.

Recently, Werfel and colleagues²⁰ described a subtype of AD in adults that is characterized by a worsening of dermatitis provoked by environmental allergens. These authors reported that exposure to pollen was associated with exacerbation of eczema in the head and neck areas. To date, no clinical trials have identified any specific therapeutic approach for this subset of patients that varies from the strategies currently in routine use. Some weak evidence suggests that oral antifungal agents could be helpful in a subset of adult patients with predominant head and neck involvement, as *Malassezia* has been hypothesized to play a role in this presentation.²¹

Clues to Consider a Differential Diagnosis

The differential diagnosis of AD is well known to pediatric and dermatology health care providers (**Table**). This list is important to consider in patients with a lesion morphology or distribution that is not typical for AD, in patients who do not respond to treatment, in those with a history of significant infections, and in cases of failure to thrive.

Disease Severity

In the majority of children, AD is mild; according to data from population-based surveys, up to one-third of parents report moderate to severe signs and symptoms in their children with

AD. The severity of AD in older children and adults has long been thought to be greater than that in young children, but data to support this view are lacking.

The factors that determine disease severity are unclear, but existing data indicate that early age of onset—that is, onset of signs and symptoms before 12 months of age—is a relatively strong predictor of severe AD.²² Other important predictors that have become recognized are the presence of an *FLG* mutation and concomitant immunoglobulin E (IgE) sensitization early in life.

Disease Course

Although most large birth cohort studies reveal that the majority of children with AD do not have disease persisting into adulthood, the true relapsing and remitting course of the disease is difficult to capture accurately in large studies. At least a subset of individuals in cohort studies whose disease “remits” likely have a persistent atopic tendency which, later in life, manifests intermittently with signs and symptoms. This group includes adults who are defined as having “sensitive skin,” but because they may not have had active eczematous signs and symptoms, they are not diagnosed with adult AD.

Recently, Margolis and colleagues²³ found that symptoms of AD actually may persist longer than previously thought. Their analysis of a registry of children with mild to moderate diseases showed that 50% of patients continued with symptoms of AD until 20 years of age.

Comorbidities

The course of AD is not defined solely by the inflammatory skin disease but also includes a high likelihood of associated comorbidities. Several comorbidities for AD are traditionally recognized, including the so-called allergic comorbidities—allergic asthma, allergic rhinitis, and food allergy. Children with AD have at least a twofold increased risk for these comorbidities.²⁴ The risk for developing comorbidities—and the severity of those associated conditions—appears to correlate directly with the severity of the skin disease.²⁴

Emerging Views on Food Allergy in Patients With AD

Food allergies are the most common allergies in children with AD, most commonly involving cow’s milk, chicken eggs, peanuts, wheat, soy, nuts, and fish.^{25,26} In a large, retrospective population-based study in the United States, the prevalence of food allergy has been reported to be slightly greater than 15% in patients with AD.^{24,27} In moderate-to-severe childhood AD, the incidence of food allergy is approximately 35%.²⁸ Previous guidelines for preventing food allergy recommended avoidance of antigenic foods in high-risk populations. However, epidemiologic studies from Lack’s group²⁹ found a lower level of peanut allergy in populations who had early exposure to peanuts.

An important advance in understanding the development of peanut allergy, specifically, in patients with AD, came from the Learning Early About Peanut Allergy (LEAP) study, a randomized controlled trial of the early introduction of peanuts in children at high risk for developing food allergy.³⁰ Young children with either an egg allergy or severe AD comprised the population identified for LEAP. In this study, children were randomized to one of two groups: peanut consumption at 4 to 11 months of age or peanut avoidance. (Children who had demonstrated skin prick wheal sizes greater than 4 mm were excluded from enrollment.) At 5 years

TABLE Differential Diagnosis of Atopic Dermatitis

Autosomal recessive hyperimmunoglobulin E syndrome (AR-HIES)
Benign cephalic histiocytosis
Contact dermatitis (irritant or allergic; consider bathing products, moisturizers)
Cutaneous T-cell lymphoma
Immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome
Langerhans cell histiocytosis
Netherton syndrome (severe erythroderma, failure to thrive)
Nummular dermatitis
Psoriasis (rash in napkin distribution, which is not typical for atopic dermatitis)
Pediatric herpes simplex virus infection
Scabies (papular and nodular, affecting palm and sole)
Seborrheic dermatitis
Severe combined immunodeficiency (SCID)
<i>Staphylococcus aureus</i> infection
Wiskott-Aldrich syndrome (bleeding disorder, low platelet count)
Zinc deficiency

of age, the children were tested for food allergy by oral food challenge. The investigators found a significant reduction in food allergy in the early consumption group. As a result of the LEAP study findings, several groups of investigators are studying whether broad-scale population interventions may be appropriate to decrease the risk for peanut allergy.

For children at highest risk for developing food allergy, clinical guidance on intervention incorporating these new findings has led an interim guidance document on feeding of peanuts.³¹ Based on the findings in these studies, an expert panel convened by the National Institute of Allergy and Infectious Diseases (NIAID) is revising the previously published guidelines. The revised guidelines are expected to address whether children with severe AD and/or egg allergy should be considered for early peanut feeding. Because patients with very high skin prick reactivity were excluded from the LEAP study, data suggest that it may be appropriate to screen infants with severe AD for IgE reactivity using either serum IgE and/or skin prick testing. It is likely that the revised NIAID guidelines will provide detailed recommendations for regular peanut exposure to try to minimize the development of peanut allergy in these patients.

Additionally, it did not appear that AD was affected differentially in the two groups in the LEAP study patients—that is, the course of AD did not seem to be affected whether patients had been fed or avoided peanuts. This finding provides support for abandoning the traditional notion that avoidance of certain foods based on specific IgE or skin prick testing without clinical correlation improves AD, or that ingesting certain foods necessarily exacerbates the disease.

AD and Infectious Diseases

It is widely known that patients with AD have an increased risk for skin infections, primarily with *Staphylococcus* organisms.³² Microbiome studies have confirmed that AD flares are associated with *Staphylococcus aureus* colonization, and also have demonstrated that AD flares are associated with changes in microbiome diversity.^{33,34} Although patients with AD are not necessarily at high risk for infection, they may have a tendency to demonstrate more severe infections with herpesviruses, human papillomaviruses, molluscum contagiosum virus, and *Malassezia* species.³⁵ One avenue of insight into these more recent observations about herpetic infections, in particular, comes from Atopic Dermatitis Research Network (ADRN) investigators, who have published human clinical studies suggesting the possibility of a genetic predisposition for eczema herpeticum through variations in gene-regulating and interferon pathways.³⁶

Association Between AD and Obesity

The association between AD and obesity was suggested by observational studies of worldwide increases in both AD and obesity.^{37,38} In a retrospective, practice-based, case-controlled study, Silverberg and colleagues³⁹ reviewed the randomly selected records of 414 children and adolescents (age range, 0 to 21 years) with AD and 828 age-matched controls. They concluded that children were more predisposed to AD when obesity started before 2 years of age and when it was prolonged for more than 2.5 years. They also noted that obese children had more severe AD. Another retrospective, case-controlled study, in an adult population of 2,090 patients in an allergy clinic, showed that the prevalence of AD was higher in obese patients; it was not

increased in obese patients with asthma, allergic rhinoconjunctivitis, or food allergies without concomitant AD.⁴⁰

More robust evidence of the AD/obesity association came from cohort of Irish children in which the PEA POD whole-body plethysmography device⁴¹ was used to determine body composition in newborns.⁴² The babies with a higher percentage of body fat had a higher rate of AD, beginning early in life.

In addition, Zhang and Silverberg⁴³ published the results of a systematic review and meta-analysis of literature examining the AD/obesity relationship. They found that the association was significant in North American and Asian populations but not in Europeans.

Future large-cohort, prospective studies are required to confirm both the AD/obesity association and the possibility that weight control, beginning at an early age in patients with AD, may help to mitigate or reverse AD symptoms.

Other AD Comorbidities

Evidence is emerging on the role of AD in the development of psychosocial and mental health comorbidities in both children and adults. Some studies suggest that such AD comorbidities may include attention-deficit/hyperactivity disorder, autism, anxiety disorder, and depression.⁴⁴ Further studies using strict definitions are required to firmly establish the relationship between mental health diagnoses and AD. Itching and sleep loss may lead to a premature diagnosis of a mental disorder that is purely transient in nature and resolves with adequate control of the skin disease.

In addition, associations between AD and a number of other conditions have been reported in some databases; these include hypertension, cardiovascular disease, rheumatoid arthritis, osteoporosis, fractures, dental problems, alopecia areata, vitiligo, and a propensity for falling.^{44,45} However, replication of these findings is required in long-term, longitudinal studies before any of these associations can be further considered as true comorbidities of AD.

Conclusion

AD is a complex disorder involving skin barrier function abnormalities and skin inflammation. Given the urban rural gradient identified from epidemiologic studies, studies are under way on the role in AD development of environmental factors such as early microbial exposures and environmental pollutants. Interest in the prevalence, causes, and prevention of atopic and nonatopic comorbidities also is increasing.

Studies such as the LEAP study reveal that epidemiologic findings can provide the impetus for randomized controlled trials that help guide clinicians in patient care. For example, promoting early food antigen exposure rather than food avoidance may dramatically reduce the burden of food allergy in patients with severe AD. Future studies on the epidemiology of AD will focus on better defining the natural course of the disease, better understanding of the associated comorbidities, and testing novel approaches to disease prevention.

References

1. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI; ISAAC Phase Three Study Group. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol*. 2009;124:1251-1258.e23.
2. Mallol J, Crane J, von Mutius E, et al; ISAAC Phase Three Study Group. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: A global synthesis. *Allergol Immunopathol (Madr)*. 2013;41:73-85.

3. Williams H, Robertson C, Stewart A, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *J Allergy Clin Immunol*. 1999;103:125-138.
4. Schram ME, Tedja AM, Spijker R, Bos JD, Williams HC, Spuls PI. Is there a rural/urban gradient in the prevalence of eczema? A systematic review. *Br J Dermatol*. 2010;162:964-973.
5. Wang I-J, Wang J-Y, Yeh K-W. Childhood atopic dermatitis in Taiwan. *Pediatr Neonatol*. 2016;57:89-96.
6. Xu F, Yan S, Li F, et al. Prevalence of childhood atopic dermatitis: An urban and rural community-based study in Shanghai, China. *PLoS ONE*. 2012;7:e36174.
7. Riedler J, Braun-Fahrlander C, Eder W, et al. Exposure to farming in early life and development of asthma and allergy: A cross-sectional survey. *Lancet*. 2001;358:1129-1133.
8. Karvonen AM, Hyvarinen A, Gehring U, et al; PASTURE Study Group. Exposure to microbial agents in house dust and wheezing, atopic dermatitis and atopic sensitization in early childhood: A birth cohort study in rural areas. *Clin Exp Allergy*. 2012;42:1246-1256.
9. McFadden JP, Basketter DA, Dearman RJ, Puangpet P, Kimber I. The hapten-atopy hypothesis III: The potential role of airborne chemicals. *Br J Dermatol*. 2014;170:45-51.
10. Thyssen JP, Zirwas MJ, Elias PM. Potential role of reduced environmental UV exposure as a driver of the current epidemic of atopic dermatitis. *J Allergy Clin Immunol*. 2015;136:1163-1169.
11. Kathuria P, Silverberg JI. Association between small particle air pollution, climate and childhood eczema prevalence and severity: A US population-based study. *Pediatr Allergy Immunol*. 2016 Feb 4. doi:10.1111/pai.12543. [Epub ahead of print]
12. Brown SJ, McLean WHI. One remarkable molecule: Filaggrin. *J Invest Dermatol*. 2012;132:751-762.
13. Rodriguez E, Baurecht H, Herberich E, et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: Robust risk factors in atopic disease. *J Allergy Clin Immunol*. 2009;123:1361-1370.e7.
14. 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.
15. Bisgaard H, Simpson A, Palmer CNA, et al. Gene-environment interaction in the onset of eczema in infancy: Filaggrin loss-of-function mutations enhanced by neonatal cat exposure. *PLoS Med*. 2008;5:e131.
16. Ownby DR, Johnson CC. Does exposure to cats or dogs early in life alter a child's risk of atopic dermatitis? *J Pediatr*. 2011;158:184-186.
17. Kelleher M, Dunn-Galvin A, Hourihane JO'B, 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.
18. Horimukai K, Morita K, Narita M, et al. Transepidermal water loss during infancy can predict the subsequent development of atopic dermatitis regardless of filaggrin mutations. *Allergol Int*. 2016;65:103-108.
19. Hamblly EM, Wilkinson DS. Sur quelques formes atypiques d'eczéma chez l'enfant. *Ann Dermatol Venerol*. 1978;105:369-371.
20. Werfel T, Heratizadeh A, Niebuhr M, et al. Exacerbation of atopic dermatitis on grass pollen exposure in an environmental challenge chamber. *J Allergy Clin Immunol*. 2015;136:96-103.
21. Kaffenberger BH, Mathis J, Zirwas MJ. A retrospective descriptive study of oral azole antifungal agents in patients with patch test-negative head and neck predominant atopic dermatitis. *J Am Acad Dermatol*. 2014;71:480-483.
22. Ben-Gashir MA, Seed PT, Hay RJ. Predictors of atopic dermatitis severity over time. *J Am Acad Dermatol*. 2004;50:349-356.
23. Margolis JS, Abuabara K, Bilker W, Hoffstad O, Margolis DJ. Persistence of mild to moderate atopic dermatitis. *JAMA Dermatol*. 2014;150:593-600.
24. Silverberg JI, Simpson EL. Association between severe eczema in children and multiple comorbid conditions and increased healthcare utilization. *Pediatr Allergy Immunol*. 2013;24:476-486.
25. Lack G. Update on risk factors for food allergy. *J Allergy Clin Immunol*. 2012;129:1187-1197.
26. Bergmann MM, Caubet J-C, Boguniewicz M, Eigenmann PA. Evaluation of food allergy in patients with atopic dermatitis. *J Allergy Clin Immunol Pract*. 2013;1:22-28.
27. Spergel JM, Boguniewicz M, Schneider L, Hanifin JM, Paller AS, Eichenfield LF. Food allergy in infants with atopic dermatitis: Limitations of food-specific IgE measurements. *Pediatrics*. 2015;136:e1530-e1538.
28. Tsakok T, Marrs T, Mohsin M, et al. Does atopic dermatitis cause food allergy? A systematic review. *J Allergy Clin Immunol*. 2016;137:1071-1078.
29. DuToit G, Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol*. 2008;122:984-991.
30. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372:803-813.
31. Fleischer DM, Sicherer S, Greenhawt M, et al. Consensus communication on early peanut introduction and prevention of peanut allergy in high-risk infants. *Pediatr Dermatol*. 2016;33:103-106.
32. Hon KL, Tsang YC, Pong NH, Ng C, Ip M, Leung TF. Clinical features and *Staphylococcus aureus* colonization/infection in childhood atopic dermatitis. *J Dermatolog Treat*. 2016;27:235-240.
33. Kong HH, Segre JA. Skin microbiome: Looking back to move forward. *J Invest Dermatol*. 2012;132:933-939.
34. Kong HH, Oh J, Deming C, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res*. 2012;22:850-859.
35. Hata TR, Gallo RL. Antimicrobial peptides, skin infections and atopic dermatitis. *Semin Cutan Med Surg*. 2008;27:144-150.
36. Gao PS, Leung DY, Rafaels NM, et al. Genetic variants in interferon regulatory factor 2 (IRF2) are associated with atopic dermatitis and eczema herpeticum. *J Invest Dermatol*. 2012;132:650-657.
37. Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*. 2006;368:733-743.
38. Hersoug LG, Linneberg A. The link between the epidemics of obesity and allergic diseases: Does obesity induce decreased immune tolerance? *Allergy*. 2007;62:1205-1213.
39. Silverberg JI, Kleiman E, Lev-Tov H, et al. Association between obesity and atopic dermatitis in childhood: A case-control study. *J Allergy Clin Immunol*. 2011;127:1180-1186.
40. Silverberg JI, Silverberg NB, Lee-Wong M. Association between atopic dermatitis and obesity in adulthood. *Br J Dermatol*. 2012;166:498-504.
41. Ellis KJ, Yao M, Shypailo RJ, Orlando A, Wong WW, Heird WC. Body-composition assessment in infancy: Air-displacement plethysmography compared with a reference 4-compartment model. *Am J Clin Nutr*. 2007;85:90-95.
42. O'Donovan SM, O'B Hourihane J, Murray DM, et al. Neonatal adiposity increases the risk of atopic dermatitis during the first year of life. *J Allergy Clin Immunol*. 2016;137:108-117.
43. Zhang A, Silverberg JI. Association of atopic dermatitis with being overweight and obese: A systematic review and meta-analysis. *J Am Acad Dermatol*. 2015;72:606-616.
44. Simpson EL. Comorbidity in atopic dermatitis. *Curr Dermatol Rep*. 2012;1:29-38.
45. Schmitt J, Schwarz K, Baurecht H, et al. Atopic dermatitis is associated with an increased risk for rheumatoid arthritis and inflammatory bowel disease, and a decreased risk for type 1 diabetes. *J Allergy Clin Immunol*. 2016;137:130-136.

Review of Critical Issues in the Pathogenesis of Atopic Dermatitis

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Abstract

About a decade ago, loss-of-function mutations in the filaggrin molecule were first implicated in the pathogenesis of ichthyosis vulgaris and, subsequently, of atopic dermatitis and other atopic diseases. Since then, intensive study of the role of filaggrin null mutations have led to other milestones in understanding the pathologic pathways in these diseases, including the initiation, maintenance, and promotion of the disease processes. The result has been new and emerging clinical and pharmacologic strategies for early identification of and intervention in atopic diseases.

Semin Cutan Med Surg 35(supp5):S89-S91

© 2016 published by Frontline Medical Communications

Keywords

Atopic dermatitis; eczema; filaggrin; filaggrin null mutation; ILC2s; interleukin-13; interleukin-25; nuocytes; toll-like receptors; type 2 innate lymphoid cells

Recent findings in the pathophysiologic mechanisms involved in the propensity for and clinical expression of atopic dermatitis (AD) have led to modifications of treatment strategies as well as new and emerging therapies.

Genetics and AD

In a recent paper, Paternoster and colleagues¹ described the results of the largest AD genetics study to date, a meta-analysis

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Publication of this CME/CE article was jointly provided by University of Louisville and Global Academy for Medical Education, LLC, and is supported by an educational grant from Anacor Pharmaceuticals, Inc.

Dr Irvine has received an honorarium for his participation in this activity. He acknowledges the editorial assistance of Joanne Still, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal article.

Alan D. Irvine, MD, *Consultant:* Anacor and Genentech, Inc.

Lawrence F. Eichenfield, MD, *Consultant:* Anacor, Genentech, Otsuka America Pharmaceutical, Inc., Pierre Fabre Laboratories, TopMD, Inc., Valeant Pharmaceuticals North America LLC. *Investigator:* Astellas Pharma US Inc., Regeneron Pharmaceuticals, Inc. *Advisory Board:* Valeant. *Speakers Bureau:* Valeant.

Sheila F. Friedlander, MD, *Consultant:* Sandoz USA. *Grant/Research:* Valeant, Merz, Inc.

Eric L. Simpson, MD, MCR, *Consultant:* Anacor, Celgene Corporation, Galderma Laboratories, L.P., MedImmune, Pfizer Inc., Sanofi-Regeneron, Valeant. *Grant/Research:* Anacor, Amgen Inc., Celgene, Chugai Pharma USA, Inc., Dermira, Inc., Eli Lilly and Company, MedImmune, Merck & Co., Inc., Roche-Genentech, Sanofi-Regeneron, Tioga Pharmaceuticals.

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of studies from European, African, Japanese, and Latino populations. More than 15 million genetic variants were involved in 21,399 patients with AD and 95,464 controls. Previously, 21 genetic susceptibility loci had been described in AD; this group identified an additional 10 AD risk loci, including genes involved in innate host defenses, T-cell function, and autoimmunity.

Although filaggrin (*FLG*) loss-of-function mutations are the strongest and best-replicated genetic links to AD worldwide (outside of Africa), the specific *FLG* mutation spectrum has been found to differ among populations. In the Han Chinese population of Singapore,² at least 25 mutations have been found. In contrast, in Europe, five mutations account for 95% of all *FLG* mutations. About 1 in 10 individuals of European ancestry carry one *FLG* null mutation, meaning that such individuals have only about half of the normal *FLG* protein in their skin, resulting in dry skin and/or ichthyosis vulgaris and a high risk for AD. In addition, about 1 in 400 individuals of European ancestry carry two *FLG* null mutations, meaning that such individuals have no *FLG* protein in the skin and have severe ichthyosis vulgaris and a very high risk for AD.³

Studies of specific populations show that genetic defects in the epidermis and the development of atopic diseases are not limited to *FLG* mutations. For example, *FLG* mutations are uncommon in African populations. A study of 100 amaXhosa children in South Africa with severe AD and ichthyosis vulgaris symptoms revealed no *FLG* mutations.⁴ A similar study in Ethiopia showed one child with an *FLG* mutation among 75 studied.⁵ African Americans are a poorly studied population with respect to AD genetics; however, *FLG* mutations that are identified in African Americans with AD are the same as those seen in European populations (about 25% of the African American genome is European).⁶

In another study, immune-mediated skin inflammation was found to be similar in severe AD in patients with and without an *FLG* mutation.⁷ Furthermore, *FLG* protein is secondarily downregulated in severe AD,⁸ through mechanisms that are not yet fully understood, although multiple cytokines are likely involved.⁹

Environmental Factors and Immunity

Several new, key findings in immunology research in the past 5 to 10 years hold promise for clarifying the complex mechanisms involved in AD pathophysiology.

Disruption of the skin barrier activates the adaptive immune alarm system; several cytokines have been identified in this process, including interleukin (IL)-33, thymic stromal lymphopoietin (TSLP), IL-25, toll-like receptors, and other inflammasome-activating signals. In genetically susceptible individuals, downstream activation of adaptive immunity results in expression of AD symptoms.

Food Allergy in Patients With Atopic Dermatitis

The association between food allergy and severe atopic dermatitis (AD) has long been recognized, and the conditions coexist in approximately one-third of children.¹ In an international study of more than 2,100 children with active AD who came from families with atopic disease histories, Hill and colleagues² showed that early onset of severe AD in infancy was associated with a high risk for immunoglobulin-E (IgE) food sensitization, which is commonly associated with food allergy. As shown in the figure below, children who had severe AD in the first year of life had a high risk for food allergies, especially to cow's milk, eggs, and fish.

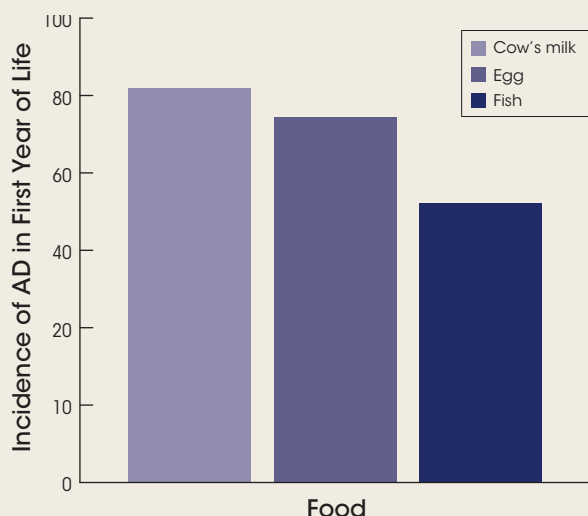


FIGURE Risk for Food Allergy Among Infants With Severe AD.

AD=atopic dermatitis.

Source: Hill et al.²

With the identification of, and increased research interest in, the presence of filaggrin (*FLG*) loss-of-function mutations in AD, a similar mechanism was hypothesized for food allergy. Brown and colleagues³ demonstrated that *FLG* loss-of-function mutations are strongly associated with IgE-mediated peanut allergy, an association that remained statistically significant in their study even after the investigators controlled for coexistent AD.

Additional research is required to further explore the association between AD and food allergy.

References

1. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics*. 1998;101:E8.
2. Hill DJ, Hosking CS, de Benedictis FM, et al; EPAAC Study Group. Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: An international study. *Clin Exp Allergy*. 2008;38:161-168.
3. 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.

Another important advance was the discovery of type 2 innate lymphoid cells (ILC2s), “first responders” in the skin. In 2010, several groups simultaneously described what were then called nuocytes, found to secrete IL-13.¹⁰ Later, ILC2s also were found to secrete IL-25, another key cytokine.¹¹

More recent data demonstrate that the populations of ILC2s expand massively in the skin of individuals with AD, as well as in those with asthma and nasal polyposis. Saunders and colleagues¹² further characterized the role of ILC2s in the diseases of the atopic march. This group found that mice deficient in *FLG* developed a skin inflammation analogous to AD (and driven by innate immunity), then later developed compromised lung function (a process resulting from adaptive immunity). These researchers demonstrated that, in the absence of the development of adaptive immunity, *FLG*-deficient mice had spontaneous, AD-like skin inflammation but did not progress to compromised lung function.

Recently published work by Jarrett and colleagues¹³ focusing on ILC2s has further elucidated the role of CD1a. CD1a-positive cells in the skin have been shown to be down-regulated by *FLG*; withdrawal of *FLG* immune suppression results in CD1a control of the inflammatory process. In addition, this article shows that the house dust mite allergens (Der p1 and Der p2) drive CD1. This work reveals both an additional pathophysiologic mechanism and another potential therapeutic target. (Currently, CD1a antibodies are available, but their use is limited to resistant Langerhans cell histiocytosis.^{14,15}) Although much remains to be understood, the importance of interactions between an “alarmed” skin barrier leading to ILC2 activation and expansion within the skin—with expression of IL-13 and subsequent recruitment of activated T cells, leading to further IL-13/IL-4 expression—is emerging as a driving pathway in this disease. Analysis of the transcriptome in AD using mRNA arrays have shown the relevance of IL-17 in chronic AD lesions, an effect seen particularly strongly among Asians with AD.¹⁶

The concept of cutaneous lymphoid stress was demonstrated by Strid and colleagues¹⁷ in a mouse model. These investigators showed that stressing the skin barrier and applying an allergen simultaneously triggers a T helper cell type 2 (T_H2) response. The imbalance in T-cell subsets in AD—predominantly T_H2 —results in expression of IL-4, IL-5, and IL-13, as well as so-called “pruritus-specific” cytokine IL-31.¹⁸ In patients with chronic AD, T_H2 activation persists, but activation of T_H1 cells also occurs. T_H2 cytokines downregulate expression of epidermal differentiation proteins (including *FLG*) as well as lipids.

New Insights and Emerging Treatments

Newer and emerging treatments are targeted toward various, specific aspects of inflammation.

In a seminal study on the topic, Hanifin and colleagues¹⁹ described increased phosphodiesterase (PDE) activity in patients with AD. Increased PDE was demonstrated in peripheral blood leukocytes of individuals with AD compared to normal controls. PDE, localized in macrophages, lymphocytes, and neutrophils, has been shown to decrease cyclic adenosine monophosphate (cAMP), causing a generalized overexpression of many proinflammatory cytokines. This led to the proposal that PDE-4 inhibition might be anti-inflammatory and to the development of the topical boron-

based small molecule PDE-4 inhibitor, crisaborole; phase III trials of this agent have been completed, and publication of the results are pending.

The oral PDE-4 inhibitor apremilast was evaluated for the treatment of AD in a pilot study, with good results²⁰; it also is being evaluated in clinical trials. Apremilast currently is approved for the treatment of moderate to severe plaque psoriasis. The IL-12/IL-23p40 antagonist, ustekinumab, also currently approved for the treatment of moderate to severe plaque psoriasis as well as psoriatic arthritis, is being investigated in AD. In addition, one case report has been published on the use of this agent for severe, refractory AD in an adolescent patient.²¹

The results of phase II trials with another new agent, dupilumab, showed promising results,²² and the results of recently completed phase III trials are pending publication. Dupilumab targets the IL-4 and IL-13 receptor α chain.

With the goal of providing an improved treatment for managing AD-associated pruritus, an IL-31 receptor antagonist, nemolizumab, is being evaluated in phase II clinical trials; an IL-31 antagonist is in an earlier stage of development. Other pharmacologic targets currently being investigated include inhibitors of TSLP, chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRT_H2), IL-13 alone, IL-22, and immunoglobulin E. Further discussion of these agents and other new and emerging therapies for AD can be found in the article on the next page.

Conclusion

Numerous studies within the past decade have provided valuable insights into the pathophysiology of AD and the other diseases that comprise the triad known as the atopic march. In AD, the existence of a skin barrier abnormality has been implicated, but genetic, environmental, and immunologic factors combine to create a complex and heterogeneous clinical picture of onset of the disease, as well as its severity and course. It is clear that skin barrier events are important in AD pathogenesis; it is becoming evident that correct identification of a barrier defect early in life may alter the natural course of AD and perhaps related phenotypes as well. Once AD develops, a number of secondary immunologic events, which maintain and promote the disease, are likely targets for pharmacologic intervention.

References

1. Paternoster L, Standl M, Waage J, et al; for the Early Genetics and Lifecourse Epidemiology (EAGLE) Eczema Consortium. Multi-ancestry genome-wide association of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. *Nat Genet*. 2015;47:1449-1456.
2. Zhang H, Guo Y, Wang W, Shi M, Chen X, Yao Z. Mutations in the filaggrin gene in Han Chinese patients. *Allergy*. 2011;66:420-427.
3. Irvine AD, McLean WHI, Leung DYM. Filaggrin mutations associated with skin and allergic diseases. *N Engl J Med*. 2011;365:1315-1327.
4. Thawer-Esmail F, Jakasa I, Todd G, et al. South African amaXhosa patients with atopic dermatitis have decreased levels of filaggrin breakdown products but no loss-of-function mutations in filaggrin. *J Allergy Clin Immunol*. 2014;133:280-282.
5. Winge MC, Bilcha KD, Liedén A, et al. Novel filaggrin mutation but no other loss-of-function variants found in Ethiopian patients with atopic dermatitis. *Br J Dermatol*. 2011;165:1074-1080.
6. Bryc K, Durand EY, Macpherson M, Reich D, Mountain JL. The genetic ancestry of African Americans, Latinos, and European Americans across the United States. *Am J Hum Genet*. 2015;96:37-53.
7. Dajnoki Z, Béke G, Mócsai G, et al. Immune-mediated skin inflammation is similar in severe atopic dermatitis patients with or without filaggrin mutation. *Acta Derm Venereol*. 2015 Nov 5. doi:10.2340/00015555-2272. [Epub ahead of print]
8. Kezic S, O'Regan GM, Yau N, et al. Levels of filaggrin degradation products are influenced by both filaggrin genotype and atopic dermatitis severity. *Allergy*. 2011;66:934-940.

9. McAleer MA, Irvine AD. The multifunctional role of filaggrin in allergic skin diseases. *J Allergy Clin Immunol*. 2013;131:280-291.
10. Neill DR, Wong SH, Bellosi A, et al. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. *Nature*. 2010;464:1367-1370.
11. Hammad H, Lambrecht BN. Barrier epithelial cells and the control of type 2 immunity. *Immunity*. 2015;43:29-40.
12. Saunders SP, Moran T, Floudas A, et al. Spontaneous atopic dermatitis is mediated by innate immunity, with the secondary lung inflammation of the atopic march requiring adaptive immunity. *J Allergy Clin Immunol*. 2016;137:482-491.
13. Jarrett R, Salio M, Lloyd-Lavery A, Subramaniam S. Filaggrin inhibits generation of CD1a neolipid antigens by house dust mite-derived phospholipase. *Sci Transl Med*. 2016 Feb 10;8(325):325ra18. doi:10.1126/scitranslmed.aad6833.
14. Kelly KM, Pritchard J. Monoclonal antibody therapy in Langerhans cell histiocytosis—Feasible and reasonable? *Br J Cancer*. 1994;70(suppl 23):S54-S55.
15. Murray S, Rowlinson-Busza G, Morris JF, Chu AC. Diagnostic and therapeutic evaluation of an anti-Langerhans cell histiocytosis monoclonal antibody (NA1/34) in a new xenograft model. *J Invest Dermatol*. 2000;114:127-134.
16. Suárez-Fariñas M, Ungar B, Correa da Rosa J, et al. RNA sequencing atopic dermatitis transcriptome profiling provides insights into novel disease mechanisms with potential therapeutic implications. *J Allergy Clin Immunol*. 2015;135:1218-1227.
17. Strid J, Sobolev O, Zafirova B, Polic B, Hayday A. The intraepithelial T cell response to NKG2D-ligands links lymphoid stress surveillance to atopy. *Science*. 2011 December 2; 334(6060): doi:10.1126/science.1211250.
18. Lebwohl MG, Del Rosso JQ, Abramovits W, et al. Pathways to managing atopic dermatitis: Consensus from the experts. *J Clin Aesthet Dermatol*. 2013;6(suppl7):S2-S18.
19. Hanifin JM, Chan SC, Cheng JB, et al. Type 4 phosphodiesterase inhibitors have clinical and in vitro anti-inflammatory effects in atopic dermatitis. *J Invest Dermatol*. 1996;107:51-56.
20. Samrao A, Berry TM, Goreschi L, Simpson EL. A pilot study of an oral phosphodiesterase inhibitor (apremilast) for atopic dermatitis in adults. *Arch Dermatol*. 2012;148:890-897.
21. Wlodek C, Hewitt H, Kennedy CT. Use of ustekinumab for severe refractory atopic dermatitis in a young teenager. *Clin Exp Dermatol*. 2016 Apr 15. doi:10.1111/ced.12847. [Epub ahead of print]
22. Thaçi D, Simpson EL, Beck LA, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: A randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet*. 2016;387:40-52.

Assessing the New and Emerging Treatments for Atopic Dermatitis

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Abstract

The newer and emerging treatments for atopic dermatitis (AD) focus on blockade of inflammatory cytokines, especially those that derive from T helper cell type 2 (T_H2) and are associated with a pathway of immunoglobulin E (IgE) sensitization. Among the proinflammatory cytokines that have been identified as promising therapeutic targets are chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRTL2), IgE, thymic stromal lymphopoietin (TSLP), and several monoclonal antibodies that block key cytokine pathways in the innate immune response. Two agents that have been studied in phase III clinical trials are the boron-based phosphodiesterase-4 (PDE-4) inhibitor, crisaborole, and dupilumab, an antibody that inhibits the interleukin-4/IL-13 receptor α chain.

Semin Cutan Med Surg 35(sup5):S92-S96

© 2016 published by Frontline Medical Communications

Keywords

Atopic dermatitis; crisaborole; dupilumab; interleukin inhibitors; petrolatum; skin barrier

A large body of work has been published within the past decade providing newer insights on the pathophysiology of and immunologic factors involved in atopic dermatitis (AD). Research has demonstrated that AD is a

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Publication of this CME/CE article was jointly provided by University of Louisville and Global Academy for Medical Education, LLC, and is supported by an educational grant from Anacor Pharmaceuticals, Inc.

Dr Eichenfield has received an honorarium for his participation in this activity. He acknowledges the editorial assistance of Joanne Still, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal article.

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disease of both skin barrier dysfunction and T helper cell type 2 (T_H2)-driven inflammation, and that it is commonly associated with other atopic diseases, including food and respiratory allergies (Figure). These insights have been used as the foundation for more recent work to explore improved strategies for prevention, early intervention, and amelioration of AD.

Early Therapy and AD Prevention

Research has shown that the skin barrier is an important site for both the initiation of AD and allergic sensitization to protein antigens.¹ A wide range of potential preventive measures have been explored, with varying results. One AD prevention strategy that is supported by convincing evidence is enhancement of the skin barrier beginning in infancy.

Consistent with pathogenesis studies showing that increased transepidermal water loss (TEWL) in infancy is associated with an increased risk for AD, a preliminary study—called the Barrier Enhancement for Eczema Prevention (BEEP) study—was conducted to determine the feasibility of performing an early intervention study of emollient use in high-risk patients that would begin in infancy.² The primary endpoint of the feasibility study was to determine whether families would be willing to have their children randomized to a group that received no emollient application (unless the child's skin was clinically dry) or to an intervention group. Infants in the intervention group were to receive daily applications of topical emollients, starting at 3 weeks of age and continuing throughout the duration of the study.

In addition to determining that 42% of families agreed to be randomized, the team also collected data on the development of AD in both the intervention and control groups. Although this was a small sample size and the study was not designed to determine AD prevention or safety of daily emollient use, the investigators reported a large reduction in risk for AD development in the emollient group. In addition, they found that emollients were well tolerated, and no differences in adverse events were noted between the emollient and no emollient groups.

Other authors also have reported beneficial results from use of emollients beginning in infancy.^{3,4} These findings have prompted the launch of larger trials in both the United States and the United Kingdom. If these studies confirm the efficacy and safety of emollient therapy, this simple and low-cost intervention has the potential to reduce the global burden of allergic diseases.

New and Emerging Therapies for AD

The rationale for the development of new and emerging treatments for AD is the blockade of known inflammatory mediators. To date, the cytokines that have been identified as important in AD are those that derive from T_H2 cells, namely interleukin (IL)-4, IL-5, and IL-13, which are associated with increased production of immunoglobulin E (IgE) and, subsequently, IgE sensitization. However, the clinical efficacy of

blocking a specific cytokine or other inflammatory mediator must be tested for each molecule. For example, although tumor necrosis factor (TNF) is expressed in skin and bone cells, TNF blockade has not been shown to be effective in established AD.⁵ However, several proinflammatory molecules involved in AD that have been identified as promising therapeutic targets include phosphodiesterase-4 (PDE-4), chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRT_H2), IgE, thymic stromal lymphopoietin (TSLP), and several monoclonal antibodies that block key cytokine pathways in the innate immune (T_H2) response, including IL-4/IL-13 receptor α chain, IL-13 alone, IL-22, and IL-31.

Although a number of novel agents for the treatment of AD currently are in development, this article addresses in depth only those for which phase III studies have been completed or are nearing completion, and briefly discusses several agents that are being tested in phase II clinical studies (Table).

PDE-4 Inhibitors

Since 1996, research has shown that PDE activity is increased and intracellular cyclic adenosine monophosphate (cAMP) levels are decreased in the peripheral blood leukocytes of patients with AD.⁶ The goal of inhibiting PDE is to increase intracellular cAMP levels and reduce cytokine mediator release. Both topical and systemic PDE-4 inhibitors have been investigated for the treatment of AD.

A topical PDE-4 inhibitor, crisaborole, integrates a boron ring into the cyclic structure of this agent. This low-molecular-weight compound effectively penetrates skin and accesses target cells. The addition of boron is thought to increase stability and have an impact on the target-binding capacity and selectivity of crisaborole.

Boron is a chemical element present in high concentrations in common foodstuffs (including chickpeas, almonds, beans, and apples); the skin absorption levels of boron are similar for crisaborole and dietary intake of boron-containing foods.

In an open-label phase IIa study, Tom and colleagues⁷ studied the safety, tolerability, and pharmacokinetic profile of crisaborole topical ointment 2% in 23 adolescents, 12 to 17 years of age, with AD lesions involving between 10% and 35% body surface area (BSA). The patients applied the ointment twice daily to affected areas, for a total of 28 days.

One patient discontinued the study because of application site dermatitis. Application site pain (in three patients) and nasopharyngitis (in three patients) were the most commonly reported adverse events; 19 adverse events were reported in 10 patients. The efficacy measures were mean Investigator's Static Global Assessment (ISGA) score and AD sign and symptom severity score. Assessment at day 29 showed that eight patients (35%) had achieved an ISGA score of 1 or lower, with at least a 2-grade improvement; the mean treatable BSA in the study population was reduced to 8.2% from a baseline of 17.6%. Blood samples for pharmacokinetic study were collected on days 1, 2, 4, 6, 8, and 9; no significant drug-related laboratory abnormalities were seen, and minimal serum levels of crisaborole were reported.

In another phase IIa study,⁸ two comparable target lesions were treated in adults with mild to moderate AD. The patients were randomized in a double-blind assignment to apply either crisaborole ointment 2% or vehicle twice daily for 28 days to one of the two target lesions. The primary efficacy endpoint was a change from baseline in the Atopic

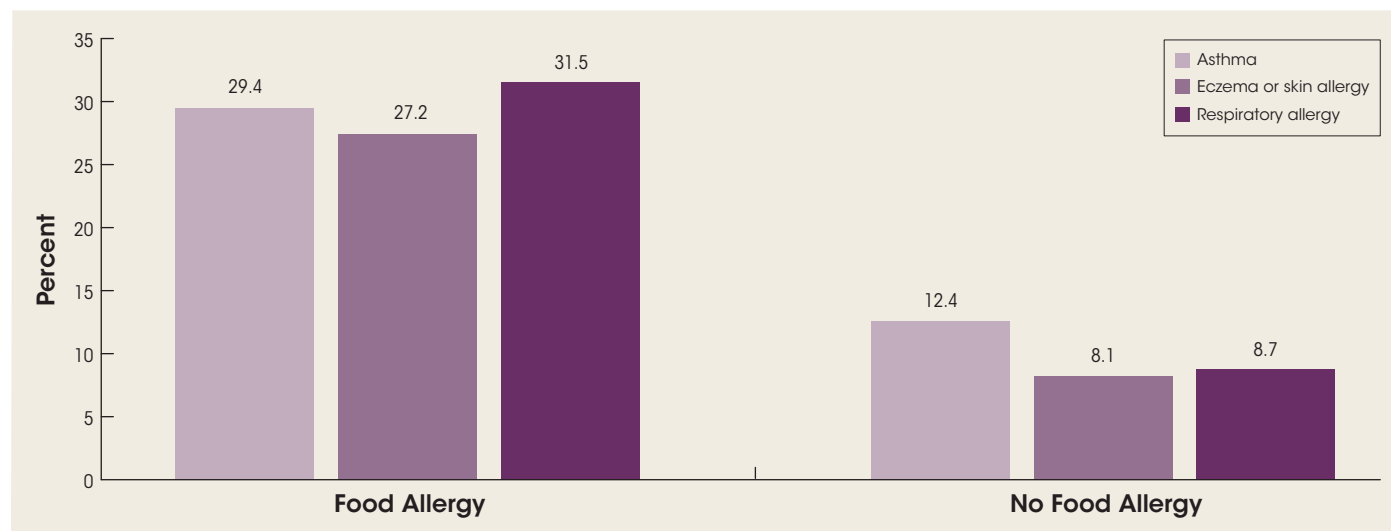


FIGURE Comorbid Food Allergy and Asthma, Eczema or Skin Allergy, or Respiratory Allergy in Previous 12 Months Among Children <18 Years of Age (%)

According to data reported by the National Center for Health Statistics, a National Health Interview Survey of about 9,500 children <18 years of age showed that an estimated 3 million (3.9%) reported having a food allergy within the past 12 months. These data, collected over a 10-year period (1997-2007), showed that children with food allergy are two to four times more likely to have related comorbidities such as asthma and other allergies. Approximately 27% of children with food allergy reported having atopic dermatitis or skin allergy; 8% of children without food allergy had such comorbidities. More than 30% of those with food allergy also had a respiratory allergy; 9% of children without food allergy had a respiratory allergy. The data also showed that children <5 years of age had higher rates of reported food allergy compared with those between 5 and 17 years of age, with boys and girls having similar rates of food allergy.

Source: Branum AM, Lukacs SL. Food allergy among U.S. children: Trends in prevalence and hospitalizations. NCHS data brief, no 10. Hyattsville, MD: National Center for Health Statistics. 2008.

TABLE New and Emerging Treatments for Atopic Dermatitis: Agents in Phase II or Phase III Clinical Trials

Compound	Mechanism of Action	Route of Administration
Currently in or completed phase III trials		
Crisaborole	PDE-4 inhibition	Topical
Dupilumab	IL-4/IL-13 receptor α -chain antagonism	SC injection
Currently in or completed phase II trials		
Apremilast	PDE-4 inhibition	Oral
Fevipiprant (QAW039)	CRT _H 2 antagonism	Oral
ILV-094	IL-22 antagonism	IV infusion
Lebrikizumab	IL-13 antagonism	SC injection
Ligelizumab (QGE031)	IgE antagonism	SC injection
Nemolizumab (CIM331)	IL-31 receptor antagonism	SC injection
OPA-15046	PDE-4 inhibition	Topical
Q301	CRT _H 2 antagonism	Topical
Tezepelumab (AMG157)	TSLP antagonism	IV infusion
Tralokinumab	IL-13 antagonism	SC injection
Ustekinumab	IL-23 p40 antagonism	SC injection
CRT _H 2=chemoattractant receptor-homologous molecule expressed on T _H 2 cells; IgE=immunoglobulin E; IL=interleukin; PDE=phosphodiesterase; SC=subcutaneous; T _H 2=T helper cell type 2; TSLP=thymic stromal lymphopoietin. Sources: ClinicalTrials.gov. Lauffer F, Ring J. Target-oriented therapy: Emerging drugs for atopic dermatitis. <i>Expert Opin Emerg Drugs</i> . 2016;21:81-89. Eczema Therapies in Development; National Eczema Association. https://nationaleczema.org/research/phases-drug-development . Accessed May 19, 2016.		

Dermatitis Severity Index (ADSI) score at day 28. At day 28, 17 of the 25 patients who received the study medication (68%) had a greater decrease in the ADSI score in the crisaborole-treated lesion than in the lesion treated with vehicle only; 5 patients (20%) had a greater decrease in the ADSI score in the vehicle-treated lesion than in the crisaborole-treated lesion. Three patients (12%) reported local application site reactions. No serious or severe adverse events were reported, and no patient discontinued the study because of an adverse event.

Two phase III, pivotal trials of crisaborole ointment 2% have been completed, involving a combined total of more than 1,000 patients treated with the study medication and more than 500 patients in vehicle groups. The average age of the patients in these studies was 12 years (range, 2 to 80 years of age). About one-third of the enrolled patients had mild AD and two-thirds had moderate AD; the mean BSA was about 20%.

The primary endpoint for treatment success (clear or almost clear skin plus two grades of improvement, with a statistically significant difference between the active-treatment and vehicle groups) was met in both phase III trials. An early separation of crisaborole versus vehicle response was seen as early as day 8, with a continued separation of response observed during the course of the study. The improvements in the different

objective signs of eczema were statistically significantly superior to the vehicle.

Treatment-emergent events, reported in about 11% of patients, included AD, application site pain, and, in a small percentage of patients, application site infection.

To date, long-term safety data that have been collected for 1 year—filed after completion of the phase III studies—appear to show that crisaborole has good tolerability and a low level of adverse events. Application site pain was observed, consistent with what was seen in the phase III studies. No significant adverse events were reported that were considered to be treatment-related. Importantly, no evidence of atrophy, telangiectasia, or hypopigmentation has been seen to date with the use of topical crisaborole ointment 2%. Other topical PDE-4 agents currently are in earlier stages of development.

The oral PDE-4 inhibitor, apremilast, currently approved by the US Food and Drug Administration (FDA) for the treatment of psoriasis, was studied in two open-label phase II trials to examine whether PDE-4 blockade could mediate the inflammatory cycle in AD. In one proof-of-concept study of 10 patients with either AD or contact dermatitis, the investigators found the medication to be safe, but efficacy results were described by the authors as “minimally effective.”⁹ In a second

study, Samrao and colleagues¹⁰ found promising results on clinical measures of efficacy; on gene ontology analyses, the investigators documented beneficial treatment-related alterations in immune response compared to baseline. A phase II multicenter, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study of apremilast in patients with moderate to severe AD was completed in February 2016; results have not yet been published.

Anti-Interleukin-4 Receptor α -Chain Antagonist

Dupilumab, a subcutaneously administered anti-IL-4R α antibody, inhibits both IL-4 and IL-13 signaling by inhibiting the IL-4 receptor α subunit. This agent has shown promising results in a broad set of phase I and II studies in adults with AD.

Thaçi and colleagues¹¹ conducted a randomized, placebo-controlled, dose-finding, 16-week, phase IIb trial testing changes in both dose and frequency of administration. A total of 380 patients with moderate to severe AD whose symptoms were not adequately controlled with topical medications were randomized into six groups to receive 300 mg dupilumab every week (n=64), every 2 weeks (n=63), or every 4 weeks (n=65); or 200 mg every 2 weeks (n=61); 100 mg every 4 weeks (n=65), or placebo (n=61); 379 patients received at least one dose of the study drug.

The Eczema Area and Severity Index (EASI) at week 16 showed a 73% improvement in the high-dose group (ie, 300 mg per week) versus 18% improvement in the placebo group, a significant improvement ($P<0.0001$). However, lower doses also resulted in statistically significant improvements ($P<0.0001$ for all active-treatment groups) over placebo, although with proportionately lower percentages of EASI improvements. At the lowest dosage—100 mg every 4 weeks—EASI improvement was 44%.

Similar rates of treatment-emergent adverse events were seen in the dupilumab and placebo groups: 81% versus 80%, respectively; serious treatment-emergent adverse event rates were 4% in the dupilumab group versus 7% in the placebo group. The number of infectious adverse events was low in both the active-treatment and placebo groups. However, herpes simplex virus infections were seen in 26 of 318 patients (8%) in the dupilumab group and in 1 of 61 patients (2%) in the placebo group.

Two phase III, 16-week trials of dupilumab in patients with mild to moderate AD have been completed, and topline results have been announced by the manufacturer. The studies, LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2, identical in design, involved a total of 1,379 patients whose AD was not adequately controlled with topical agents or who were not candidates for topical medication.

The enrollment criteria included a score of 3 or 4 on the 5-point Investigator's Global Assessment (IGA) scale (0=clear to 4=severe); patients also were assessed at baseline using EASI and other measures of AD. Patients were randomized to receive dupilumab, 300 mg once weekly; dupilumab, 300 mg every 2 weeks; an initial loading dose of 600 mg of dupilumab, followed by placebo for 16 weeks; or placebo.

In the 300 mg/week dupilumab groups in SOLO 1 and SOLO 2, 37% and 36% of patients, respectively, achieved IGA scores of 0 or 1 (clear or almost clear); in the groups who received 300 mg every 2 weeks, IGA 0 or 1 was achieved in 38% and 36%, respectively. In the placebo groups in SOLO

1 and 2, IGA 0 or 1 was seen in 10% and 8.5% of patients, respectively ($P<0.0001$ for these treatment- vs placebo-group comparisons).

Improvements over baseline in EASI were 72% and 69%, respectively, in patients who received dupilumab, 300 mg per week, in SOLO 1 and 2. EASI improvements were 72% and 67%, respectively, in patients who received dupilumab, 300 mg every 2 weeks, in SOLO 1 and 2. In the placebo groups, in both studies, EASI improvements were 38% and 31% ($P<0.0001$ for these treatment- vs placebo-group comparisons).

A 75% improvement in EASI (EASI-75) was seen in 52.5% and 48%, respectively, of patients who received the 300-mg weekly dosage of dupilumab in SOLO 1 and 2. EASI-75 was seen in 51% and 41%, respectively, of those who received dupilumab 300 mg every 2 weeks. In the placebo groups, 15% and 12% of patients, respectively, in SOLO 1 and 2 achieved EASI-75 ($P<0.0001$ for these treatment- vs placebo-group comparisons).

The overall rates of adverse events during the treatment period were 65% and 73% in the dupilumab groups in SOLO 1 and 2, and 65% and 72% in the placebo groups, respectively. Serious adverse events were seen in 1% and 3% of patients in the dupilumab groups, and 5% and 6% in the placebo groups. Injection site reactions and conjunctivitis were seen more often in the treatment groups; no patient discontinued the study because of an injection site reaction, and one patient dropped out because of conjunctivitis.

Interleukin-13 Inhibitors

Interleukin-13 has been shown to be highly expressed in AD skin on immunohistochemistry and transcriptome studies, and IL-13 gene polymorphisms are associated with increased AD risk. The rationale for the development of lebrikizumab and tralokinumab, IL-13 cytokine inhibitors, is that direct inhibition of IL-13 will have a therapeutic effect in AD. Both agents currently are undergoing phase II studies.

Thymic Stromal Lymphopoietin Antagonist

Tezepelumab, an inhibitor of thymic stromal lymphopoietin (TSLP), currently is being investigated in phase II studies. The cytokine TSLP is released by epithelial cells and keratinocytes (and, to a lesser extent, dendritic cells) during the process of allergen-related inflammation. TSLP has been shown to induce expression of IL-4, leading to a robust T_H2 response; the result of this process is upregulation of TSLP receptors and the consequent development of a positive feedback loop.¹²

Interleukin-31 Inhibitors

Several agents that inhibit IL-31 are currently being studied. One, nemolizumab (CM331), has progressed to phase II trials, with promising preliminary data¹³; others are in earlier stages of study. IL-31, which is secreted by activated T cells, has been identified as the key cytokine involved in causing pruritus.¹⁴ Some evidence also suggests that IL-31 may contribute to the development of AD.

Interleukin-22 Inhibitor

The IL-22 inhibitor, fezakinumab, is being studied in phase II trials in adults with AD. IL-22 has been found to be produced by CD4⁺ and CD8⁺ T-cell populations, referred to as T22; these cytokines are significantly increased in the skin of patients with AD.

Interleukin-12/23p40 Inhibitor

Ustekinumab, an IL-12/23p40 inhibitor approved for the treatment of psoriasis and psoriatic arthritis, is being studied as a treatment for AD in adults.¹⁵ The phase II study was completed recently, and publication of results is pending. A recent case report suggests the potential efficacy of ustekinumab in severe childhood AD.¹⁶

Janus Kinase Inhibitors

A phase IIa trial of topical tofacitinib was conducted in which the Janus kinase inhibitor was shown to substantially improve EASI in adult patients with mild to moderate AD.¹⁷ The use of oral tofacitinib for severe AD has been reported in an open-label study.¹⁸

Vitamin D

It is known that cathelicidins in the skin are relatively deficient in individuals with AD, and that vitamin D may mediate the expression of innate cathelicidins in the skin, although the literature is mixed on the possible mechanisms involved. Several intervention studies have been published on the possible effects on AD of oral vitamin D supplementation; these studies have yielded mixed results.¹⁹⁻²¹

Melatonin Supplementation

Chang and colleagues²² examined the possible role of melatonin in AD for its effects on sleep and disease severity in a double-blind, placebo-controlled, crossover trial of 48 children with more than 5% BSA involvement. The intervention was melatonin 3 mg/day for 4 weeks, with a 2-week washout and a crossover. The primary outcome measure was AD severity measured on the Scoring Atopic Dermatitis (SCORAD) index. Secondary outcomes included sleep variables such as sleep-onset latency and decreased mobility during sleep. The investigators reported a statistically significant difference in the SCORAD index (95% CI, -13.7 to -4.6; $P < 0.001$) with the use of melatonin. Improvements also were seen in sleep patterns, with decreases in both sleep-onset latency and mobility during sleep.

It is important to note that sleep improvement with melatonin can be seen in any population; this effect cannot be considered specific to AD. In addition, the statistically significant difference seen in the SCORAD index requires some closer consideration: the baseline SCORAD index was 49, indicating the highest level of moderate AD, on the border of severe AD; post-intervention, the SCORAD was 40, which is still at the highest level of moderate AD and on the border of severe AD. Thus, the study population had AD that was not optimally managed with this intervention. Nevertheless, it will be interesting to see future work using melatonin as adjuvant therapy in this population compared to traditional antihistamines.

Conclusion

Through research in animal models, several likely pathways for targeted treatment have been identified, and several new and emerging medications hold promise for the treatment of AD. In addition, early intervention to protect the skin barrier may be an effective method of preventing AD onset in genetically susceptible patients.

References

1. Lack G. Update on risk factors for food allergy. *J Allergy Clin Immunol*. 2012;129:1187-1197.
2. Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol*. 2014;134:818-823.
3. Mason JM, Carr J, Buckley C, et al. Improved emollient use reduces atopic eczema symptoms and is cost neutral in infants: Before-and-after evaluation of a multifaceted educational support programme. *BMC Dermatol*. 2013;13:7.
4. Horimukai K, Morita K, Narita M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(4):824-830.
5. Montes-Torres A, Llamas-Velasco, Pérez-Plaza A, Solano-López G, Sánchez-Pérez J. Biological treatments in atopic dermatitis. *J Clin Med*. 2015;4:593-613.
6. Hanifin JM, Chan SC, Cheng JB, et al. Type 4 phosphodiesterase inhibitors have clinical and in vitro anti-inflammatory effects in atopic dermatitis. *J Invest Dermatol*. 1996;107:51-56.
7. Tom WL, Van Syoc M, Chanda S, Zane LT. Pharmacokinetic profile, safety, and tolerability of crisaborole topical ointment, 2% in adolescents with atopic dermatitis: An open-label phase 2a study. *Pediatr Dermatol*. 2016;33:150-159.
8. Murrell DF, Gebauer K, Spelman L, Zane LT. Crisaborole topical ointment, 2% in adults with atopic dermatitis: A phase 2a, vehicle-controlled, proof-of-concept study. *J Drugs Dermatol*. 2015;14:1108-1112.
9. Volf EM, Au SC, Dumont N, Scheinman P, Gottlieb AB. A phase 2, open-label, investigator-initiated study to evaluate the safety and efficacy of apremilast in subjects with recalcitrant allergic contact or atopic dermatitis. *J Drugs Dermatol*. 2012;11:341-346.
10. Samrao A, Berry TM, Goreski R, Simpson EL. A pilot study of an oral phosphodiesterase inhibitor (apremilast) for atopic dermatitis in adults. *Arch Dermatol*. 2012;148:890-897.
11. Thaçi D, Simpson EL, Beck LA, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: A randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet*. 2016;387:40-52.
12. Ziegler SF, Roan F, Bell BD, Stoklasek TA, Kitajima M, Han H. The biology of thymic stromal lymphopoietin (TSLP). *Adv Pharmacol*. 2013;66:129-155.
13. Nemoto O, Gurue M, Nakagawa H, et al. The first trial of CIM331, a humanized antihuman interleukin-31 receptor A antibody, in healthy volunteers and patients with atopic dermatitis to evaluate safety, tolerability and pharmacokinetics of a single dose in a randomized, double-blind, placebo-controlled study. *Br J Dermatol*. 2016;174:296-304.
14. Dillon SR, Sprecher C, Hammond A, et al. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat Immunol*. 2004;5:752-760.
15. Rockefeller University. Pilot study of ustekinumab for subjects with chronic atopic dermatitis. <http://clinicaltrials.gov/ct2/show/NCT01806662?term=rockefeller+eczema+stelara&rank=1>. Accessed April 19, 2016.
16. Wlodek C, Hewitt H, Kennedy CT. Use of ustekinumab for severe refractory atopic dermatitis in a young teenager. *Clin Exp Dermatol*. 2016 Apr 15. doi:10.1111/ced.12847. [Epub ahead of print]
17. Bissonnette R, Papp K, Poulin Y, et al. Efficacy and safety of topical Janus kinase inhibitor tofacitinib in the treatment of atopic dermatitis: Results of a Phase 2a randomized clinical trial. Poster presented at: World Congress of Dermatology, June 2015, Vancouver.
18. Levy LL, Urban J, King BA. Treatment of recalcitrant atopic dermatitis with the oral Janus kinase inhibitor tofacitinib citrate. *J Am Acad Dermatol*. 2015; 73:395-399.
19. Sidbury R, Sullivan AF, Thadhani RI, Camargo CA Jr. Randomized controlled trial of vitamin D supplementation for winter-related atopic dermatitis in Boston: A pilot study. *Br J Dermatol*. 2008;159:245-247.
20. Javanbakht MH, Keshavarz SA, Djalali M, et al. Randomized controlled trial using vitamins E and D supplementation in atopic dermatitis. *J Dermatolog Treat*. 2011;22:144-150.
21. Camargo CA Jr, Ganmaa D, Sidbury R, Erdenedelger KH, Radnaakhand N, Khanduren B. Randomized trial of vitamin D supplementation for winter-related atopic dermatitis in children. *J Allergy Clin Immunol*. 2014;134:831-835.
22. Chang YS, Lin MH, Lee JH, et al. Melatonin supplementation for children with atopic dermatitis and sleep disturbance: A randomized clinical trial. *JAMA Pediatr*. 2016;170:35-42.

The Changing Paradigm of Atopic Dermatitis Therapy

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Abstract

The pathophysiology of atopic dermatitis (AD) is complex, and future treatment options will likely be incorporated in a multimodal approach to management. The new, directed therapies that have been developed will likely be used in conjunction with concomitant continuous or intermittent use of standard therapies; the goal is to optimize therapeutic outcomes while minimizing adverse impacts on safety and cost. Current data regarding disease course and expression throughout life suggest that treatment strategies also will need to be adjusted as a patient grows. Research also indicates that interventions begun in infancy—such as the use of emollients—may mitigate or prevent AD signs and symptoms in children at high risk for the disease.

Semin Cutan Med Surg 35(supp5):S97-S99

© 2016 published by Frontline Medical Communications

Keywords

Atopic dermatitis; petrolatum; pimecrolimus; tacrolimus; topical calcineurin inhibitors; topical immunomodulators

Within the past 2 decades, ongoing research regarding the pathophysiology of atopic dermatitis (AD) and other conditions associated with immunoglobulin E (IgE) sensitization has resulted in an expanded and more

comprehensive understanding of the genetic, immunologic, and environmental factors involved in the onset and expression of atopic diseases.

This evidence has generated interest in multiple clinical care pathways. The importance—and possibility—of identifying and preventing disease in at-risk infants is an area of major interest. The care of patients with established disease can now include the use of new agents that are often more clearly targeted at a specific biologic pathway. Given risk-benefit ratios that include not only toxicity but also cost, better use of existing and widely used topical and systemic treatments remains an area of active investigation. New information has led to an increased ability to provide optimal management, and to meet public expectations for better disease control and quality of life for patients and their families.

However, our better understanding of both the complexity of atopic disease and the multiple therapeutic choices available increases the need for health care providers to understand the myriad options now available for both preventive and therapeutic interventions. Providers must be aware of safety and cost issues for available agents and be prepared to inform families about the range of treatment choices available as well as the evidence available to date regarding the safety of these various agents.

Considering Long-Term Treatment Safety in AD

Medications that are approved by the US Food and Drug Administration (FDA) have undergone rigorous testing for efficacy and safety, but the experience with a new medication prior to FDA approval often is relatively short-term and, compared to the anticipated, real-world experience, consists of exposure to relatively few subjects. Postmarketing surveillance over time can reveal safety signals that bear watching and, in some instances, the FDA has mandated the collection of such information in a more structured fashion, as in the case of topical calcineurin inhibitors (TCIs).

The TCIs tacrolimus and pimecrolimus were approved by the FDA—in 2000 and 2001, respectively—for the second-line treatment of patients with AD 2 years of age and older. In 2006, the FDA issued a requirement that both TCIs carry a boxed warning on their labels, cautioning prescribers and consumers about a theoretical risk for malignancy associated with these agents.

Following a meeting of the FDA Pediatric Advisory Committee in 2003, two 10-year prospective patient registries were created to track malignancies in patients with AD treated with TCIs: A Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term Safety (APPLES) of tacrolimus, initiated in 2005, and the Pediatric Eczema Elective Registry (PEER), initiated in 2004. In the protocols for both registries,

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Publication of this CME/CE article was jointly provided by University of Louisville and Global Academy for Medical Education, LLC, and is supported by an educational grant from Anacor Pharmaceuticals, Inc.

Dr Friedlander has received an honorarium for her participation in this activity. She acknowledges the editorial assistance of Joanne Still, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal article.

Sheila F. Friedlander, MD, *Consultant*: Sandoz USA, *Grant/Research*: Valeant Pharmaceuticals North America LLC, Merz, Inc.

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each patient is assessed every 6 months over a period of 10 years for any serious adverse events, including systemic and cutaneous malignancies. In the APPLES registry, the last among 8,037 patients was enrolled in 2012; the estimated date of completion is August 2022.¹ In the PEER registry, recruitment is ongoing until 2017, with an estimated total enrollment of 8,000 patients; the estimated completion date is December 2021.² The interim data from the APPLES registry are expected to be published in the first quarter of 2017.

In the decade since this warning was instituted, numerous epidemiologic and clinical studies have been published that fail to support a clear association between TCIs and malignancy, including lymphoma. Among these was an update published in 2013 by Siegfried and colleagues,³ who evaluated the preclinical, clinical, and epidemiologic evidence available to that point and concluded that an association between TCIs and malignancies was unsubstantiated. An analysis of data from the The Health Improvement Network database in the United Kingdom also has failed to detect an increased risk for malignancies with the use of TCIs.⁴

Finally, Sigurgeirsson and colleagues⁵ reported the results of their 5-year randomized, open-label trial involving 2,418 infants with AD between 3 and 12 months of age. The infants were randomized to receive pimecrolimus (with a short-term topical corticosteroid allowed to manage disease flares) or topical corticosteroids alone; 1,205 infants were in the pimecrolimus group, and 1,213 were in the corticosteroid group. The study had two objectives: primarily, to compare the safety of pimecrolimus and topical corticosteroids, and secondarily, to document the long-term efficacy—treatment success being defined as a clear or almost-clear score on the Investigator's Global Assessment.

The investigators reported that treatment success was achieved in more than 50% of patients by week 3 in both groups. After 5 years of treatment, overall treatment success in both groups was greater than 85%, and facial treatment success was 95% in both groups. The safety profile in both groups was similar, and no evidence of impairment of humoral or cellular immunity was seen in either group. The authors concluded that these findings support the use of pimecrolimus as a first-line therapy for mild to moderate AD in infants as young as 3 months of age.

Prior to the appearance of the boxed warning on TCI labeling, many clinicians were liberally—and successfully—prescribing these medications, as indicated, as a second-line, short-term agent for managing mild to moderate flares of AD in patients 2 years of age and older, particularly in treating facial and intertriginous areas. Health care providers often were prescribing TCIs off-label as longer-term, maintenance therapy to prevent flares and to treat AD in children less than 2 years of age. The institution of the boxed warning caused many clinicians to avoid TCIs and resume more frequent use of topical corticosteroids. This was detrimental to those patients who had achieved control of AD with the TCIs, particularly those with involvement of skin areas (such as the face and intertriginous areas) for which topical corticosteroids cannot be used on a prolonged basis.

Luger and colleagues⁶ recently published a consensus article that reviewed the literature on TCIs (most of which addressed pimecrolimus, specifically) and concluded that these agents are safe and effective for treating AD in infants as young as

3 months of age. They further recommended that the labeling in the United States and Europe restricting TCI use to patients 2 years of age and older be changed. In addition, they advised that the boxed warnings be removed.

Scientific Advances and Drug Development for AD

The advent of biologics greatly expanded the treatment options for immune-mediated diseases. The discovery of the role of inflammatory cytokines in rheumatoid and psoriatic arthritis as well as cutaneous psoriasis and the introduction of tumor necrosis factor inhibitors for these diseases provided a much-needed alternative to standard therapies. However, they also introduced new concerns regarding both safety and cost. Since that time, treatment options have been introduced that target other inflammatory mediators, such as interleukins (ILs), which play key roles in many inflammatory dermatologic diseases.

Targeted treatments for AD based on pathophysiologic processes involved in AD have been developed, including the IL-4R α receptor blocker dupilumab and small-molecule phosphodiesterase-4 (PDE-4) inhibitors such as crisaborole.

However, therapeutic strategies using biologic agents and small molecules that have been successful in treating psoriasis may not work with equal efficacy in AD. Psoriasis has specific, identified molecular pathophysiologic pathways that the newer medications have targeted, whereas AD is a more heterogeneous disease with multiple genetic, immunologic, and environmental components and complex pathophysiologic pathways, all of which have been shown to vary among ethnic and geographic populations. Therefore, although newer biologic agents are welcome additional options for treating AD and, it is hoped, will lead to improved outcomes in many patients, it is unlikely that any single agent, class of agents, or therapeutic approach can be expected to be universally applicable treatments for all forms of AD. Instead, the choice of agents used in subsets of patients may be best guided by techniques that could include patient stratification based on biomarkers such as transcriptome analysis, immunohistochemistry, and serum cytokine profiling. This is a key area for future study in AD.

Renewed Attention to Existing Agents

In the current and future treatment of AD it is likely that safety and economic considerations will favor the development of better stratagems that use currently existing, traditional modalities. Such a strategy was used to improve the treatment of acute lymphoblastic leukemia (ALL): only one new medication has been developed for ALL in the last 35 years, but the patient survival rate has increased over that time from 60% to 95%, the result of optimization of existing treatments.

Traditional therapeutics that are candidates for future optimization in selected patients with AD include methotrexate, cyclosporine,⁷ and coal tar.^{8,9} The use of newer agents such as systemic biologic agents initially, with subsequent “pulsed” dosing of topical corticosteroids, in tandem or in concert with TCIs or topical PDE inhibitors, could provide patients with a therapeutic plan that maximizes response and minimizes cost and toxicity. Topical bleach baths have been found to have both anti-inflammatory as well as anti-infective properties, identifying their utility in both preventing infection and decreasing inflammation.¹⁰

In addition, newer evidence indicates that the traditional intervention of petrolatum, in an attempt to protect the skin barrier, appears also to have beneficial immunologic effects.^{11,12} Identification of at-risk infants and intervention with topical emollients and other dry skin care could prove to be an effective public health intervention, leading to the decreased incidence of disease. In addition, interventions that might be optimal in infancy may need to be modified with age and in light of changing manifestations of AD.

Conclusion

Current evidence indicates that the complex pathophysiology of AD requires a multimodal approach to management and a view toward changing strategies as a child grows. Allergen avoidance, skin barrier protection, and long-term treatment plans will necessitate ongoing patient education and skill development as patients become increasingly able to participate in the management of their disease. Therapeutic education of parents—and, in the long term, patients themselves—must include attention to AD comorbidities as more information becomes available on the effects of AD and its treatments on cardiovascular, musculoskeletal, and neurologic systems.

In addition, as new classes of therapies are presented for possible inclusion in the roster of potential treatments for AD, changes will be needed in the algorithms of care that we now use, including interventions in infancy—such as emollient use—that may prevent the manifestation of AD symptoms in children who are at risk for the disease. Judicious use of the multiple, new, directed therapies that have been developed—likely employed in conjunction with continuing or intermittent use of standard therapies—will allow practitioners to provide optimal therapy while minimizing adverse impacts on safety and cost.

References

1. Astellas Pharma Inc. A pediatric longitudinal evaluation to assess the long-term safety of Protopic for the treatment of atopic dermatitis (APPLES). <https://clinicaltrials.gov/ct2/show/NCT00475605>. Accessed April 14, 2016.
2. Valeant Pharmaceuticals International, Inc. 10 year registry of children (ages 2-17 years) with eczema that have used pimecrolimus (PEER). <https://clinicaltrials.gov/ct2/show/NCT00568997?term=PEERS+AND+pimecrolimus&rank=1>. Accessed April 14, 2016.
3. Siegfried EC, Jaworski JC, Hebert AA. Topical calcineurin inhibitors and lymphoma risk: Evidence update with implications for daily practice. *Am J Clin Dermatol*. 2013;14:163-178.
4. Arellano FM, Arana A, Wentworth CE, Fernández-Vidaurre C, Schlienger RG, Conde E. Lymphoma among patients with atopic dermatitis and/or treated with topical immunosuppressants in the United Kingdom. *J Allergy Clin Immunol*. 2009;123:1111-1116.e13.
5. Sigurgeirsson B, Boznanski A, Todd G, et al. Safety and efficacy of pimecrolimus in atopic dermatitis: A 5-year randomized trial. *Pediatrics*. 2015;135:597-606.
6. Luger T, Boguniewicz M, Carr W, et al. Pimecrolimus in atopic dermatitis: Consensus on safety and the need to allow use in infants. *Pediatr Allergy Immunol*. 2015;26:306-315.
7. Flohr C, Irvine AD. Systemic therapies for severe atopic dermatitis in children and adults. *J Allergy Clin Immunol*. 2013;132:774-774.e6.
8. van den Bogaard EH, Bergboer JGM, Vonk-Bergers M, et al. Coal tar induces AHR-dependent skin barrier repair in atopic dermatitis. *J Clin Invest*. 2013;123:917-927.
9. McLean WH, Irvine AD. Old King coal: Molecular mechanisms underlying an ancient treatment for atopic eczema. *J Clin Invest*. 2013;123:551-553.
10. Shi VY, Foolad N, Omelas JN, et al. Comparing the effect of bleach and water baths on skin barrier function in atopic dermatitis: A split-body randomized controlled trial. *Br J Dermatol*. 2016 Feb 15. doi:10.1111/bjd.14483 [Epub ahead of print]
11. Czarnowicki T, Malajian D, Khattri S, et al. Petrolatum: Barrier repair and antimicrobial responses underlying this “inert” moisturizer. *J Allergy Clin Immunol*. 2016;137:1091-1102.e7.
12. Janmohamed SR, Orange AP, Devillers AC, et al. The proactive wet-wrap method with diluted corticosteroids versus emollients in children with atopic dermatitis: A prospective, randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol*. 2014;70:1076-1082.

New Treatment Paradigms in Atopic Dermatitis: Understanding and Incorporating Recent and Emerging Therapies Post-Test

Original Release Date: June 2016 • Expiration Date: May 31, 2018

Estimated Time to Complete Activity: 2.0 hours

To get instant CME/CE credits online, go to <http://tinyurl.com/atopicdermsuppl2016>. Upon successful completion of the online test and evaluation form, you will be directed to a Web page that will allow you to receive your certificate of credit via e-mail or you may print it at that time. If you have any questions or difficulties, please contact the Global Academy for Medical Education office at info@globalacademycme.com.

Questions: For each question or incomplete statement, choose the answer or completion that is correct. Circle the most appropriate response.

- 1. Epidemiologic studies have demonstrated that the prevalence of atopic dermatitis (AD):**
 - A. Has decreased worldwide, but increased in rural areas
 - B. Has increased worldwide, especially in rural areas
 - C. Has decreased worldwide, especially in urban areas
 - D. Has increased worldwide, especially in urban areas
- 2. The complex interactions between environment and filaggrin (FLG) status (ie, whether a defect in the FLG protein is present) is demonstrated in studies of pet ownership, which show that:**
 - A. Cat ownership enhances the detrimental effects of FLG mutations
 - B. Cat ownership may protect against the detrimental effects of FLG mutations
 - C. Dog ownership may enhance the detrimental effects of FLG mutations
 - D. Dog and cat ownership both enhance the detrimental effects of FLG mutations
- 3. An important cohort study by Kelleher and colleagues showed that the strongest predictor of AD development is:**
 - A. Asthma during the first year of life
 - B. Elevated transepidermal water loss (TEWL) in newborns
 - C. Peanut allergy, demonstrated by skin prick testing
 - D. Presence of an FLG mutation
- 4. FLG loss-of-function mutations are the strongest and best-replicated genetic links to AD in:**
 - A. Africa
 - B. Asia
 - C. Europe
 - D. Worldwide (outside of Africa)
- 5. Disruption of the skin barrier activates:**
 - A. The adaptive alarm system
 - B. Atopic march
 - C. Peanut allergy
 - D. Receptors for tumor necrosis factor (TNF)
- 6. Both topical and systemic inhibitors of phosphodiesterase-4 (PDE-4)—including topical crisaborole and systemic apremilast—have been investigated for the treatment of AD. The goal of inhibiting PDE is to:**
 - A. Decrease intracellular cyclic adenosine monophosphate (cAMP) levels
 - B. Decrease the need for corticosteroid use to treat AD flares
 - C. Increase intracellular cAMP levels and decrease cytokine mediator release
 - D. Increase cytokine mediator release
- 7. The monoclonal antibody dupilumab targets _____, a key cytokine pathway in the innate immune (T helper cell type 2 [T_H2]) response in patients with AD.**
 - A. Immunoglobulin E
 - B. Interleukin-4/interleukin-13
 - C. PDE-4
 - D. TNF
- 8. Among the following strategies for preventing AD, which one is supported by convincing evidence?**
 - A. Avoidance of food such as peanuts
 - B. Enhancement of the skin barrier beginning in infancy
 - C. Exposure to cats early in life
 - D. Vitamin C
- 9. Long-term data collected on patients who have used topical calcineurin inhibitors (TCIs)—ie, pimecrolimus and tacrolimus—show that:**
 - A. TCIs are associated with a modest risk for lymphoma
 - B. The theoretical association between TCIs and the risk for malignancies is not supported
 - C. These agents should not be used in children less than 2 years of age
 - D. These agents should be used only in patients with very severe AD
- 10. As reported by Shi and colleagues, a treatment strategy for AD that has both anti-inflammatory and anti-infective properties is the use of:**
 - A. Bleach baths
 - B. Coal tar
 - C. Early feedings of peanut products
 - D. Topical antibiotic ointment

*The University of Louisville thanks you for your participation in this CME/CE activity.
All information provided improves the scope and purpose of our programs and your patients' care.*

New Treatment Paradigms in Atopic Dermatitis: Understanding and Incorporating Recent and Emerging Therapies Activity Evaluation Form

Original Release Date: June 2016 • **Expiration Date:** May 31, 2018 • **Estimated Time to Complete Activity:** 2.0 hours

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. CME/CE credit letters and long-term credit retention information will only be issued upon completion of the post-test and evaluation online at: <http://tinyurl.com/atopicdermsuppl2016>.

Please indicate your profession/background: (check one)

☐ MD/DO ☐ MSN/BSN/RN ☐ PA ☐ APN/NP ☐ PharmD/RPh ☐ Resident/Fellow Researcher ☐ Administrator ☐ Student
☐ Other; specify _____

LEARNING OBJECTIVES: <i>Having completed this activity, you are better able to:</i>	Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
Discuss the most recent information on the epidemiology and pathogenesis of atopic dermatitis (AD), and how this is likely to affect the management of patients with AD.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Explain how the current and emerging understanding of filaggrin loss-of-function mutations affect the development of AD.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Recognize the rationale for and mechanisms of action of existing and emerging therapies for AD.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Analyze how existing and emerging therapies fit into the AD treatment paradigm.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
More effectively individualize patient treatment strategies by considering the full range of current and emerging therapeutic options.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

If you do not feel confident that you can achieve the above objectives to some extent, please describe why not.

Based on the content of this activity, what will you do differently in the care of your patients/regarding your professional responsibilities? (check one)

- ☐ Implement a change in my practice/workplace.
☐ Seek additional information on this topic.
☐ Do nothing differently. Current practice/job responsibilities reflect activity recommendations.
☐ Do nothing differently as the content was not convincing.
☐ Do nothing differently. System barriers prevent me from changing my practice/workplace.

If you anticipate changing one or more aspects of your practice/professional responsibilities as a result of your participation in this activity, please briefly describe how you plan to do so.

If you plan to change your practice/workplace, may we contact you in 2 months to see how you are progressing?

- ☐ Yes. E-mail address: _____
☐ No. ☐ I don't plan to make a change.

If you are not able to effectively implement what you learned in this activity, please tell us what the system barriers are (eg, institutional systems, lack of resources, etc).

OVERALL EVALUATION		Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
The information presented increased my awareness/understanding of the subject.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
The information presented will influence how I practice/do my job.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
The information presented will help me improve patient care/my job performance.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
The program was educationally sound and scientifically balanced.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Overall, the program met my expectations.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I would recommend this program to my colleagues.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Lawrence F. Eichenfield, MD	Author demonstrated current knowledge of the topic.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Author was organized in the written materials.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sheila F. Friedlander, MD	Author demonstrated current knowledge of the topic.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Author was organized in the written materials.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Alan D. Irvine, MD	Author demonstrated current knowledge of the topic.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Author was organized in the written materials.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Eric L. Simpson, MD, MCR	Author demonstrated current knowledge of the topic.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Author was organized in the written materials.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

What topics do you want to hear more about, and what issue(s) regarding your practice/professional responsibilities will they address?

Please provide additional comments pertaining to this activity and any suggestions for improvement.

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