Meeting the Challenge of Atopic Dermatitis From Infancy to Adulthood

Introduction
Practical Strategies for the Diagnosis and Assessment of Atopic Dermatitis
Atopic Dermatitis Progression: Evaluation Intervention Strategies
Nonpharmacologic Strategies and Topical Agents for Treating Atopic Dermatitis: An Update
Addressing the Immunopathogenesis of Atopic Dermatitis: Advances in Topical and Systemic Treatment

CME/CE Post-Test and Evaluation Form

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From Infancy to Adulthood

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Clinicians must remain up-to-date on the findings from clinical studies on the diagnosis and management of AD, as well as the benefits and risks of all treatment options available, to make the appropriate choices for management of their individual patients.

**Learning Objectives**

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

- Discuss the features of AD that should allow a clinical diagnosis of the condition in most patients, and list the factors in children and adults that should lead to the consideration of alternative diagnoses or identification of comorbid conditions.
- Explain how the current understanding of the role of the epidermal skin barrier and transepidermal water loss should affect—and continue to improve—the day-to-day care of patients with AD.
- More effectively individualize patient treatment strategies by considering the full range of current and emerging therapeutic options.
- Consider the evidence-based recommendations in the current guidelines for the diagnosis and treatment of AD published by the American Academy of Dermatology.
- Describe the rationales and mechanisms of action of the new and emerging therapies for AD, particularly the recently approved topical agent crisaborole and the systemic medication dupilumab (phase III study results under FDA review at the time of publication of this supplement).

**Disclosure Declarations**

Individuals in a position to control the content of this educational activity are required to disclose: 1) the existence of any relevant financial relationship with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients with the exemption of non-profit or government organizations and non-health care related companies, within the past 12 months; and 2) the identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

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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.
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Dermatologists and primary care clinicians have been able to adequately manage most patients with atopic dermatitis (AD), using long-standing and familiar nonpharmacologic and pharmacologic interventions. However, many individuals have chronic or intermittent AD that profoundly affects their quality of life, and yet remain inadequately treated.

Good skin care—hydration and moisturization—remains a cornerstone of management for all patients, for both acute and maintenance therapy, as is identification and avoidance of irritants that trigger flares. To bring AD flares under control, topical corticosteroids (TCS) often suffice. Topical calcineurin inhibitors—pimecrolimus or tacrolimus—are effective as nonsteroidal anti-inflammatory agents, both as alternatives for flare management (especially in delicate skin areas) and in maintenance regimens. Bacterial colonization and infection should be recognized and managed, and dilute bleach baths may be highly effective.

These strategies have allowed the majority of patients with AD to experience clinical improvement. It is not necessary for individuals with AD to settle for intolerable chronic signs and symptoms, only reaching out to practitioners when AD becomes acute. Recent advances in research have led to a further understanding of the pathogenesis of AD, and the treatment of this disease has evolved. The result is more effective use of standard nonpharmacologic and medical therapies, with newer medications soon to be approved or currently in development. Most individuals can and should be treated to achieve minimal disease, minimal rashes, and minimal pruritus.

Several new and emerging agents, which target immunologic pathways in AD, are now or will soon be available and represent the next important step in the evolution of treatment. Crisaborole, a topical phosphodiesterase-4 (PDE-4) inhibitor that mitigates the inflammatory process of AD, recently was approved by the US Food and Drug Administration. Dupilumab, a systemic agent that has been studied in phase III clinical trials, is an inhibitor of the interleukin (IL)-4 receptor \( \alpha \) subunit, which results in inhibition of both IL-4 and IL-13 signaling. Other immunomodulators, such as Janus kinase inhibitors, are being investigated in AD.

The newer immunologic agents join the standard, familiar strategies to provide extended disease control and an expanded expectation for an improved quality of life for patients with AD.

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Meeting the Challenge of Atopic Dermatitis From Infancy to Adulthood • globalacademycme.com/dermatology
Practical Strategies for the Diagnosis and Assessment of Atopic Dermatitis

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Abstract
Atopic dermatitis (AD) has a significant, lifelong clinical impact on affected individuals and has profound effects on quality of life both for patients and their families. The diagnosis usually can be reliably established on the basis of the history and physical examination. In patients with skin of color, blanching of the skin may be helpful to detect erythema, lichenification, follicular accentuation, and hypopigmentation (all of which are more common than in lighter-skinned patients). Once the diagnosis of AD is established, an assessment of severity, persistence, and impact on the patient’s and family’s life is important as a guide to treatment decisions.

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Keywords
Atopic dermatitis; eczema

The prevalence of atopic dermatitis (AD) in the United States is about 3% to 5% in the overall population, or approximately 15 million children and adults. The current lifetime prevalence of AD in childhood is estimated to be 10% to 15%, which is an increase of 6% to 10% over the last 30 years.1-5 In addition, AD prevalence among children differs according to geography. In the United States, prevalence varies markedly by region, from a low of 8.7% in Florida to a high of 18.05% in Maryland. These differences may be the result of environmental and other factors such as sun exposure, baseline humidity, and urban/rural gradients.7

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Diagnosis of AD
The diagnosis of patients with characteristic signs and symptoms of AD usually does not present a clinical challenge. The typical findings include pruritus, erythema, papules/vesicles, xerosis, excoriations, erosions, and, in many cases, lichenification and dyspigmentation. Questioning during the history taking also provides important diagnostic information: Is the rash chronic or atypical (suggesting another diagnosis or the presence of a comorbid condition)? Does the rash flare and remit (the hallmark history in a patient with AD)? Finally, a positive family history for AD—in either or both parents—increases the likelihood that a child has AD.

The characteristic, age-related anatomic distribution of AD provides further evidence to support the diagnosis.8,9 In infants, the face (particularly the cheeks and chin), trunk, and extensor extremities are the most common sites of involvement, with sparing of the diaper area. In toddlers and older children, the most commonly affected sites are the flexor areas of the wrists, ankles, and antecubital and popliteal fossae. In adolescents and adults, the wrists, hands, neck, and ankles are typically affected.

Several clinical features may be associated with AD and may suggest or support the diagnosis (Table 1), although their presence is not specific for AD.10

Differential Diagnosis
In the few cases in which the diagnosis of AD cannot be determined clinically, a number of other common disorders may be considered in the differential diagnosis (Table 2).

Seborrheic dermatitis (cradle cap) is particularly common in infants from birth to 6 months of age, and represents a potentially confounding finding, as seborrheic dermatitis and eczematous dermatitis often cannot be differentiated in this age group. Diffuse cradle cap in the presence of eczematous dermatitis on the arms and cheeks may resolve over time or may evolve into AD, despite eventual clearance of the cradle cap.

TABLE 1 Findings Possibly Associated With Atopic Dermatitis

| The presence of the following conditions may be associated with atopic dermatitis (AD), although they are not specific for AD: |
| Hyperlinear palms |
| Ichthyosis |
| Keratosis pilaris |
| Ocular or periorbital changes |
| Perifollicular accentuation |
| Pityriasis alba |
| Prurigo lesions |


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**Contact dermatitis** is an alternative diagnosis, or it may be a comorbid condition. Careful questioning of the caregiver regarding exposure to potential irritants can help determine whether contact dermatitis might be the culprit or a contributor, and contact allergy testing may be necessary.

**Nummular dermatitis** can present with discreet, annular pruritic eczematous plaques, often with crusting.

The other common disorders in the differential diagnosis usually can be recognized and distinguished from AD based on characteristic signs, symptoms, and history.

Some findings and differences from typical atopic dermatitis disease course should prompt consideration of a broader differential diagnosis than atopic dermatitis, depending on a patient’s age (summarized in Table 3). In an infant or young child, consideration of a differential diagnosis of rare disorders—metabolic, nutritional, genetic, immune, and proliferative conditions (Table 4)—becomes especially important when a growth curve abnormality/failure to thrive is noted, when multiple cutaneous and/or systemic infections occur, when the morphology or distribution of a rash is unusual, when a patient’s response to typical AD treatment is poor, or when fixed-plaque hypopigmentation is treated and then recurs in the same site and in the same configuration, which suggests the possibility of cutaneous T-cell lymphoma.

In adults, late-onset AD signs and symptoms should prompt consideration of other diagnoses in addition to AD (Table 5).

### Clinical Variations in AD in Skin of Color

In patients with Fitzpatrick skin types IV, V, and VI, the cutaneous signs that are classic for AD in patients with lighter skin may not be evident (Figure). For example, erythema can be especially hard to detect on simple visual inspection (redness may be appreciated on skin blanching).

Lichenification and follicular accentuation are more common in skin of color, as are hypopigmentation and/or hyperpigmentation. In some cases, hypopigmentation can be profound, causing patients and families to be concerned that the change in skin coloration represents scarring and/or a side effect of a topical medication. They should be reassured that pigment changes associated with AD are common and are the result of inflammation in the skin.

In addition, certain features of AD, such as xerosis, may have a different appearance in skin of color. The presence of some nonspecific findings that may be associated with AD can be helpful in making the diagnosis in patients with darker skin.

*Pityriasis alba* is commonly seen in individuals with dark skin, although it may occur in these patients in the absence of AD. *Perifollicular accentuation* and *prurigo lesions* also are common in patients with skin of color. Because filaggrin mutations are associated with hyperlinear palms and a tendency toward skin dryness, *hyperlinearity* suggests a diagnosis of AD.

### TABLE 2 Differential Diagnosis of Atopic Dermatitis: Common Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact dermatitis (allergic and irritant)</td>
</tr>
<tr>
<td>Ichthyosis vulgaris</td>
</tr>
<tr>
<td>Keratosis pilaris</td>
</tr>
<tr>
<td>Nummular dermatitis</td>
</tr>
<tr>
<td>Psoriasis</td>
</tr>
<tr>
<td>Scabies</td>
</tr>
<tr>
<td>Seborrheic dermatitis</td>
</tr>
<tr>
<td>Tinea corporis</td>
</tr>
</tbody>
</table>

### TABLE 3 Findings Which Should Prompt Reconsideration of the Diagnosis of Atopic Dermatitis in Infants and Young Children

<table>
<thead>
<tr>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to thrive</td>
</tr>
<tr>
<td>Multiple infections, cutaneous and/or systemic</td>
</tr>
<tr>
<td>Unusual morphology or distribution of rash</td>
</tr>
<tr>
<td>Poor response to typical atopic dermatitis (AD) treatments</td>
</tr>
<tr>
<td>Fixed-plaque hypopigmentation</td>
</tr>
<tr>
<td>Late-onset AD signs/symptoms</td>
</tr>
</tbody>
</table>

### TABLE 4 Rare Disorders to Be Considered in the Differential Diagnosis of Atopic Dermatitis in Infants and Children

<table>
<thead>
<tr>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic/nutritional/genetic disorders</td>
</tr>
<tr>
<td>Acrodermatitis enteropathica</td>
</tr>
<tr>
<td>Eosinophilic gastroenteritis</td>
</tr>
<tr>
<td>Gluten-sensitive enteropathy</td>
</tr>
<tr>
<td>Hurler syndrome</td>
</tr>
<tr>
<td>Netherton syndrome</td>
</tr>
<tr>
<td>Omenn syndrome</td>
</tr>
<tr>
<td>Other nutritional deficiencies (biotin, essential fatty acids)</td>
</tr>
<tr>
<td>Phenylketonuria</td>
</tr>
<tr>
<td>Prolidase deficiency</td>
</tr>
<tr>
<td>Zinc deficiency (prematurity; deficient breast milk zinc; cystic fibrosis)</td>
</tr>
<tr>
<td>Immune disorders</td>
</tr>
<tr>
<td>Agammaglobulinemia</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
</tr>
<tr>
<td>Hyperimmunoglobulin E syndrome</td>
</tr>
<tr>
<td>Neonatal lupus erythematosus</td>
</tr>
<tr>
<td>Severe combined immunodeficiency disorder</td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
</tr>
<tr>
<td>Proliferative disorders</td>
</tr>
<tr>
<td>Langerhans cell histiocytosis</td>
</tr>
</tbody>
</table>
Assessment of AD

Once the diagnosis of AD is established, an assessment of severity, persistence, and impact on the patient’s and family’s life is important as a guide to treatment decisions.

Clinical Assessment

Severity. About one-third of children with AD have severe disease, which can be predicted by three main factors: onset of signs and symptoms before 1 year of age, the presence of a filagrin gene mutation, and concomitant immunoglobulin E (IgE) sensitization early in life. The degree of severity is judged on the basis of extent of involvement (the body surface area affected), qualities of the lesions, the persistence of the disease, and the impact of AD on a patient’s and family’s quality of life.

Persistence is defined by cycles of remission and relapse of signs and symptoms. Patients whose AD responds readily to standard treatment modalities and who experience prolonged periods of remission with occasional flares of signs and symptoms are considered to have less severe disease than those whose AD is difficult to bring under control and who relapse frequently.

Impact of disease. Clinicians should ask questions that probe quality-of-life challenges for the patient and the family, such as sleep disturbance, interference with school and/or work, effects on relationships, and disruption of family life.

Assessment Tools and Laboratory Tests for AD

Tests of AD severity that have been developed for use in clinical trials—the Eczema Area and Severity Index (EASI) and SCOring Atopic Dermatitis (SCORAD)—and patient assessment measures such as the Patient-Oriented Eczema Measure (POEM) and the Patient-Oriented SCOring Atopic Dermatitis (PO-SCORAD) take a great deal of time to use and may not be suitable for use in clinical practice.

Laboratory tests that are sometimes performed to assess AD—namely, IgG testing for food allergies and gluten sensitivity testing—are of no clinical value. In the past, some clinicians had advocated the use of allergen-specific IgE tests as part of an assessment for allergies that might be “causing the eczema,” but more recent studies have demonstrated that these tests have poor predictive value, with a high probability of false-positive results. Studies have shown IgE testing for food allergy to have poor predictive value, with skin-prick tests only marginally more useful.11,12 These tests may be useful when evaluating for specific food responses in suspected allergies.

Follow-Up Evaluation: Practical Questions

At follow-up visits, useful information can be obtained about recent routines for skin care and medication use during the previous week, rather than just asking about use since the last visit. In assessing topical medication use, it is often helpful to ask how long a tube of the patient’s medication lasts.

Other questions should elicit information relating to the period since the last visit, including the last time the patient’s skin was totally clear, whether any systemic medications (such as oral prednisone) have been prescribed by another clinician, and whether the patient has been hospitalized for any reason or has been seen by a clinician in another specialty, such as an allergist.

Finally, each clinical interaction should include an assessment of how the patient and/or the family think about AD. The simple question “What are you afraid of concerning this skin condition?” can elicit a focused answer with useful information.

Conclusion

Atopic dermatitis is a common condition that is usually easy to diagnose clinically, although considerations of a broader differential diagnosis are appropriate when the history, clinical course, or response to therapy are atypical. Evaluations of AD should include assessment of disease severity, persistence, response to therapies, and disease impact on the individual and family.

References

Atopic Dermatitis Progression: Evaluating Intervention Strategies

Linda F. Stein Gold, MD,* and Lawrence F. Eichenfield, MD†

Abstract
Several risk factors have been identified that appear to be consistently and strongly associated with the development of atopic dermatitis (AD): a family history of atopy, an inherited genetic predisposition, and active and passive exposure to tobacco smoke. Recent studies have also demonstrated that a simple intervention from birth—the daily application of an emollient moisturizer—seems to protect susceptible infants from the development of AD.

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Keywords
Atopic dermatitis; eczema; emollients; filaggrin; food allergy; inflammatory cytokines; interleukin; T helper cells

A fundamental question concerning atopic dermatitis (AD) has been the topic of many recent studies: What are the relative contributions of genetics and environment to disease susceptibility and expression?

Genetic Predisposition and Family History
Evidence for a genetic predisposition in AD comes from a variety of studies. Most recently, a study comparing AD in identical and fraternal twins demonstrated concordance rates of up to 0.86 in monozygotic and 0.41 in dizygotic pairs, providing clear evidence for a genetic predisposition to AD.1

In addition, Wen and colleagues2 reported that about 70% of patients with AD have a positive family history for atopic diseases. Previous studies had demonstrated that the chances of a patient having AD are 2- to 3-fold if one parent has AD, and 3- to 5-fold if both parents are atopic.1,4 Interestingly, Ruiz and colleagues5 demonstrated more than 2 decades ago that a maternal history of AD may be more predictive than a paternal history.

Exposure to Tobacco Smoke
A meta-analysis across 86 studies showed that both active and passive exposure to tobacco smoke increases AD risk, with an odds ratio of 1.87.6

Role of the Filaggrin Gene
The role of the filaggrin gene in the development of AD has become widely recognized within the past decade. In 2006, Irvine and McLean7 studied the histology of normal and atopic skin and demonstrated that the skin in AD has a defective barrier, with an absence of filaggrin-containing keratohyalin granules in the epidermal granular layer. These granules are known to be crucial to the formation of a tight, functional skin barrier.

Research regarding the nature and role of filaggrin has demonstrated that filaggrin is formed when profilaggrin—which is encoded by the filaggrin gene (FLG)—degrades. Later, as filaggrin itself breaks down, the resulting products contribute to the formation of natural moisturizing factor, which is important for epidermal hydration and barrier function. The absence of the filaggrin gene (ie, an FLG null mutation) is associated with a risk for the earlier onset of AD, as well as for more severe and persistent disease. Patients with an FLG null mutation have 1.2 to 13 times the risk for the development of AD.8

Although FLG mutations have been noted in patients with AD from various ethnic and geographic populations, demonstrating its importance in the pathogenesis of AD, some questions remain to be explored. For example, a substantial number of patients who have AD have no identifiable FLG mutations, whereas approximately 40% of individuals with FLG null alleles do not develop AD.8

Such questions raise the possibility that a filaggrin abnormality might develop, de novo, in patients who have no evidence of an inherited FLG mutation. Howell and colleagues9 explored this question in a study designed to determine whether FLG expression could be reduced in patients who had AD but were not carriers of any identified FLG mutations. These investigators enrolled 39 patients with no history of AD and 30 patients with moderate AD. Among their other findings, the researchers detected the presence of interleukin (IL)-4 and IL-13 in patients with AD; in these patients, keratinocytes showed significantly reduced filaggrin expression. They concluded that the patients with AD in this study had an acquired defect in filaggrin expression in the presence of an atopic inflammatory response.
AD Immunology
AD is an immunologic disorder characterized by T helper cell dysregulation, mast cell (basophil and eosinophil) hyperactivity, and immunoglobulin E (IgE) production; the latter may be a factor that occurs secondary to other events. In addition, AD is associated with an imbalance in T-cell subsets, with type 2 T helper (TH2) cells predominating. The key TH2 cytokines include IL-4, IL-5, and IL-13. In addition, a specific cytokine, IL-31, has been identified, informally referred to as the “pruritus-specific” cytokine.

Modulating Barrier Dysfunction in AD
Identification of the role of skin barrier dysfunction in patients with AD and extensive study of the underlying disease immunology has allowed investigators to explore the possibility of (1) identifying susceptible patients early in life and (2) preventing or minimizing the risk for the development of AD. Recent studies have demonstrated that both of these goals are achievable in many, if not all, patients with AD.

In a study of 1,903 newborns, Kelleher and colleagues evaluated skin barrier function at birth (on day 2) and at 2 and 6 months of age by assessing transepidermal water loss (TEWL) (so-called “leaky skin”). In addition, 1,300 infants were tested for the presence of FLG mutations. The investigators reported that 18.7% of the babies were diagnosed with AD at 6 months of age; at 12 months of age, 15.53% had AD. The upper quartile of TEWL measurement at day 2 was “significantly predictive” of an AD diagnosis at 12 months of age (P<0.05). Conversely, the lowest quartile of TEWL at day 2 was associated with protection against AD at 12 months of age. In addition, the upper quartile of TEWL measurement at 2 months of age also was significantly predictive of AD at 12 months (P<0.05). Parental AD history and infant FLG status were not factors in these results.

To explore the potential protective effects of minimizing TEWL, Simpson and colleagues enrolled infants at increased risk for AD in a preliminary study of emollient use. The Barrier Enhancement for Eczema Prevention (BEEP) study was designed to determine whether parents would be willing to have their newborns randomized to receive either no emollients (the control group) or full-body applications of topical emollients at least once daily, beginning at 3 weeks of age (intervention group). The investigators reported that 42% of families agreed to the randomization. The primary endpoint was to establish whether emollient application was a feasible strategy. In addition, data were collected on the development of AD at 6 months of age in the intervention and control groups.

The authors reported that emollient use had a statistically significant protective effect, with a relative reduction in the risk of AD of 50% (relative risk, 0.50; 95% CI, 0.28-0.9; P=0.017). No emollient-related adverse effects were reported, and no differences in adverse effects were seen between the intervention and control groups. Although this study was small and was not designed to establish efficacy and safety, the results suggest that larger, randomized controlled trials are warranted.

Meanwhile, other small studies have yielded similar findings regarding the protective effects of emollient use in infants, including a study of 136 subjects from Great Britain and a study from Japan involving 118 subjects.

Predicting Long-Term AD Persistence
Clinicians know from experience that AD resolves over time in most children, with few having persistent AD into adulthood. However, predicting which individuals will have persistent disease has not been possible. In a recently published meta-analysis of 45 studies from 15 countries (involving 110,651 patients, for a total of 434,992 patient-years), Kim and colleagues found that three main factors were involved in the risk for persistence of AD into adulthood: (1) disease in childhood that persists for 10 years or more (compared to ≤5 years); (2) onset of AD later than 2 years of age; and (3) greater vs less severity of AD in childhood.

Role of Food Allergies in AD
Because some patients with mild to moderate AD also have food allergies, many parents (and some clinicians) assume that a causative relationship exists. Although other studies estimated an AD/food allergy comorbidity incidence for mild to moderate AD of 30% to 40%, more recent evidence shows that the incidence actually is about 15% in this subpopulation of patients; the incidence of food allergy among patients with severe AD is approximately 35%. Interestingly, a review and meta-analysis of prospective studies shows that breastfeeding may decrease the incidence of AD.

The strategy of blindly eliminating commonly allergenic foods—including cow’s milk, eggs, and peanuts—from the diets of all patients with AD is not effective in modifying the course of AD. Nevertheless, food and other allergies may contribute to AD in some patients. Consider referring patients to a pediatric allergist for evaluation when AD is moderate to severe, when skin disease is recalcitrant, and in the presence of a reliable history of exacerbation after exposure to certain foods. Teenagers or adults with severe AD also may benefit from an allergy evaluation.

Recent work by Du Toit and colleagues has demonstrated that exposure to foods actually may protect children from food allergies. This study, Learning Early About Peanut Allergy (LEAP), was a randomized controlled trial of early exposure to peanuts of children at high risk for developing a food allergy. The study population in LEAP consisted of 640 infants between 4 and 11 months of age with severe eczema, egg allergy, or both. All subjects received a skin-prick test to determine sensitivity to peanuts. All patients with a negative skin-prick test were randomized to either consume or avoid peanuts. Among children with positive skin-prick tests, children with wheals of 5 mm or larger were excluded from the study; children with wheals of 1 to 4 mm were randomly assigned to either consume or avoid peanuts.

At 60 months of age, the children were tested for peanut allergy by oral challenge. Among the children with initially negative skin-prick tests, the prevalence of peanut allergy was 13.7% in the avoidance group and 1.9% in the consumption group, a statistically significant difference (P<0.001). Among the enrolled patients with an initially positive skin-prick test, the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the consumption group (P=0.004).

The results of this and other studies has led to a revision in guidelines for feeding and allergy testing in children with severe AD in the first year of life, calling for skin-prick testing or IgE screening to determine whether a child should have early peanut feeding. Dermatologists and pediatricians should collaborate with an allergist in managing the care of these patients.
Conclusion
Atopic dermatitis is a common relapsing inflammatory condition with genetic as well as environmental risk factors. New research has contributed to a better understanding of this disease and improved strategies for prevention and treatment.

References
**Nonpharmacologic Strategies and Topical Agents for Treating Atopic Dermatitis: An Update**

Linda F. Stein Gold, MD,* and Lawrence F. Eichenfield, MD†

**Abstract**
The signs and symptoms of atopic dermatitis (AD) can be safely and effectively controlled in most patients; in many cases, the disease can be improved to the point that signs and symptoms are absent or minimal. In addition, flares can be effectively controlled and, in some cases, prevented. New topical medications, improved strategies for the use of topical corticosteroids and topical calcineurin inhibitors, and judicious use of nonpharmacologic regimens—including bathing, bleach baths, and early use of emollients—have led to better disease management and improved quality of life for patients and their families.

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**Keywords**
Atopic dermatitis; bathing; bleach baths; calcineurin inhibitors, topical; corticosteroids, topical; eczema

As the body of recent literature concerning atopic dermatitis (AD) continues to reshape consensus on many aspects of patient management, clinicians should not neglect to also update our messaging to our patients. It is important for patients and families to understand several key points. First, AD can be safely and effectively controlled in most patients. Second, with the availability of new medications and better strategies for the use of medications and nonpharmacologic regimens that have been the cornerstone of AD management for many years, it is now possible for treatment to improve AD to the point of minimal to no disease and symptoms. Third, flares can be effectively controlled and, in some cases, prevented.

Patients and caregivers should know that lack of full control of signs and symptoms of AD need not and should not be simply tolerated, and visits to the clinician should not be put off until a flare occurs or until signs and symptoms progress to an unacceptable threshold of severity. Strong evidence from prospective studies, reviewed and evaluated by a panel of experts, demonstrates that some treatments for AD that have been in use for many years should still be considered valuable components of a comprehensive treatment regimen (Table).

**Bathing Frequency/Duration**
Clinicians differ on their recommendations for the frequency of bathing and duration of immersion time. Unfortunately, no good evidence is available to establish firm guidelines. Patients and caregivers who avoid daily bathing because of the perception that frequent bathing further dries already xerotic skin should understand that water does not contribute to skin dryness. Frequent—even daily or twice-daily—baths are helpful in hydrating the skin, provided that a liquid nonsoap cleanser is used that is appropriate for patients with AD and that moisturization is always included in the bathing routine—a regimen referred to as “soak and seal.” In addition, frequent bathing is especially helpful and important for patients with exudative eczema and may decrease bacterial colonization of the skin.

When inflammation is severe, applications of towels soaked in warm to hot (but not scalding) water over a topical corticosteroid agent or moisturizer can soothe discomfort and calm erythema. Application of plastic food wrap over the towels prolongs the time between resoaking and reapplication.

Experience shows that short baths, lasting 5 to 10 minutes, are best. In addition to hydrating and cleansing the skin, bathing improves penetration of topical medications and aids in debridement of infected and necrotic tissue. A moisturizer and/or emollient ointment or cream (rather than lotion) should be applied promptly after immersion, within a few minutes and while the skin is still moist.

**Infection Control**
Because the skin barrier is defective in patients with AD, patients have an increased susceptibility to infections, including viral (especially molluscum contagiosum and herpes simplex virus), fungal (tinea and Malassezia), and bacterial (Staphylococcus aureus).

*S. aureus* colonization is a common problem and poses an ongoing risk for secondary bacterial infection in patients with AD, and numerous investigators have explored strategies to manage colonization and prevent infection. In one study, Huang and colleagues demonstrated that treatment of *S. aureus* colonization can decrease the severity of AD. In that 3-month, randomized, investigator-blinded, placebo-controlled study, 31 patients between 6 months and 17 years of age with moderate to severe AD and secondary bacterial
infections received a 14-day course of oral cephalexin plus either intranasal mupirocin ointment (5 consecutive days per month) and a twice-weekly bleach bath or intranasal pimecrolimus ointment and plain water baths. The researchers found that the incorporation of bleach baths and intranasal mupirocin resulted in a statistically significant improvement in the Eczema Area and Severity Index than did the placebo regimen.

More recently, Shi and colleagues described the value of bleach baths—the addition of 4 ounces (½ cup) of household bleach to a standard-sized bathtub of water—has both anti-inflammatory and anti-infective properties, and can be helpful in both preventing infection and decreasing inflammation in susceptible patients.

Although no standard has been set for the frequency of bleach baths, it seems prudent to recommend that patients with severe AD and recurrent infections use a bleach bath at least three times weekly; consider daily bleach baths for patients with very severe AD and very frequent infection recurrences. Patients who prefer to shower rather than bathe can achieve the same benefit by using a “bleach spray”: a mixture of 1 teaspoon of household bleach in 64 ounces (a half gallon) of water, applied to the skin during the shower. Commercial sodium hypochlorite sprays are sold over-the-counter, although the mixture described is easy to prepare and is considerably less expensive.

Topical Corticosteroid Therapy Maintenance
The use of topical corticosteroid therapy to bring an acute flare of AD under control is an undisputed strategy. However, the duration of topical corticosteroid treatment is a topic of ongoing debate, with some clinicians advocating cessation of treatment once the skin is clear and others promoting the benefits of long-term maintenance therapy.

Hanifin and colleagues examined the question of topical corticosteroid maintenance in a study of 372 children and adults with moderate to severe AD. All patients were treated with fluticasone propionate cream 0.05%, twice daily for 4 weeks, plus emollients. After 4 weeks, patients were assigned to either an active-treatment group, continuing fluticasone applications on a maintenance schedule of twice weekly, or to a vehicle-only group. Hanifin et al reported that at week 20, the patients in the vehicle-only group were 7 to 8 times more likely to experience a relapse than were the patients who continued maintenance treatment with the corticosteroid.

Topical Calcineurin Inhibitors
The two currently available topical calcineurin inhibitors (TCIs), pimecrolimus and tacrolimus, have a long history of safety and efficacy in patients with AD. Unlike topical corticosteroids, these agents can be used on any affected body surface area (BSA), including the face. The efficacy and safety of these agents have been demonstrated in clinical trials.

Eichenfield and colleagues studied the efficacy and safety of pimecrolimus cream 1% vs vehicle in two 6-week, randomized, multicenter studies involving 403 children and adolescents with mild (30%), moderate (60%), and severe (9%) AD. All patients had BSA involvement of at least 5%. As early as day 8, a statistically significant improvement was seen on the investigator’s global score of clear or almost clear in the active-treatment group vs vehicle (P≤0.05).

In a 12-week randomized, double-blind, vehicle-controlled study, Paller and colleagues evaluated the safety and efficacy of tacrolimus ointment 0.03% and 0.1% in pediatric patients with moderate to severe AD. A total of 352 children between 2 and 15 years of age (mean age, 6.1 years) were enrolled; 61.5% had severe AD at baseline; 83.5% of patients had involvement of the head/face and/or neck. At week 12, significantly more patients in the tacrolimus treatment groups had clinical improvement of at least 90% than did patients in the vehicle group (P≤0.001). The authors noted that in the active-treatment groups, improvements in AD signs and symptoms, BSA affected, and patients’ assessment of pruritus were seen early in the study and were maintained through week 12. Several adverse events occurred more frequently in the higher-concentration tacrolimus treatment groups than in the vehicle group: a sensation of burning, pruritus, varicella, and blisters (the incidence of varicella and blisters was <5%). (Note that only the 0.03% concentration is approved by the US Food and Drug Administration for use in patients <15 years of age.)

Gollnick and colleagues studied pimecrolimus cream 1% in the long-term management of AD in adults, with the goal of determining the effectiveness of this agent in preventing the progression of flares. The 543 enrolled patients were at

**TABLE** Recommended Nonpharmacologic Interventions for Atopic Dermatitis*

<table>
<thead>
<tr>
<th>Moisturizers</th>
<th>Integral in atopic dermatitis (AD)</th>
<th>Strong evidence that moisturizer use can reduce disease severity and need for pharmacologic treatment</th>
<th>Should be applied soon after bathing to improve skin hydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bathing</td>
<td>Suggested as part of treatment and maintenance (no standard established for frequency or duration)</td>
<td>Addition of oils, emollients, and most other additives to bath water and use of acidic spring water are not recommended at this time (evidence insufficient)</td>
<td></td>
</tr>
<tr>
<td>Cleansers</td>
<td>Limited use of nonsoap cleansers that are neutral or low pH, hypoallergenic, and fragrance-free</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wet-wrap treatments</td>
<td>Use with or without topical corticosteroids</td>
<td>Recommended for patients with moderate to severe AD to decrease disease severity and transepidermal water loss during flares</td>
<td></td>
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</tbody>
</table>


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least 18 years of age and had mild or moderate AD. Their AD was clear or almost clear before they were randomized to receive pimecrolimus cream (n=277) or vehicle only (n=266) in this 26-week study. Twice-daily applications of the study medication (either pimecrolimus or vehicle) were started as soon as a patient had any sign or symptom of a relapse. If the disease worsened, patients were permitted to add a moderately potent topical corticosteroid after the study medication had been used for at least 3 days. The primary endpoint was the number of days elapsed before corticosteroid treatment was needed to control a flare. The investigators reported that the mean number of corticosteroid-free days was significantly higher in the active-treatment group (152 days) than in the vehicle group (138.7 days) (P<0.001); moreover, the mean number of flares requiring corticosteroid treatment was lower in the pimecrolimus group (P=0.0014).

The guidelines for topical treatment of AD note that TCIs are valuable as corticosteroid-sparing agents; TCIs should be prescribed for the treatment of actively affected areas. If necessary, a topical corticosteroid can be used with a TCI to bring an AD flare under control.

The guidelines also recommend use of these agents, proactively, for relapse prevention. The use of TCIs as maintenance therapy should be intermittent, with applications 2 or 3 times weekly on areas that commonly flare. Such use is further supported by the results of a study by Luger and colleagues, who reviewed the use of TCIs in 21 trials including 5,825 pediatric patients with AD. The authors described the safety data as “well-reported”: Less than 5% of patients reported discontinuation of TCI treatment because of adverse events; cutaneous and systemic adverse events were similar in the TCI and vehicle groups; and no cases of lymphoma were reported.

**Conclusion**

Effective control of atopic dermatitis involves a comprehensive approach utilizing good skin care principles as well as nonpharmacologic and pharmacologic treatments. Proactive management and maintenance therapy can prolong remission and provide significant relief.

**References**

Addressing the Immunopathogenesis of Atopic Dermatitis: Advances in Topical and Systemic Treatment

Lawrence F. Eichenfield, MD,* and Linda F. Stein Gold, MD†

Abstract
Several immunologic mediators—phosphodiesterase (PDE), interleukin (IL), small molecules, and Janus kinase—have been implicated in the pathogenesis of atopic dermatitis, and evidence has shown that blocking these mediators can help modify the disease process. Several new topical medications have been developed that target the enzyme PDE; crisaborole was recently approved by the US Food and Drug Administration (FDA) for the treatment of atopic dermatitis, and phase II studies have been completed on OPA-15406. The phase III clinical trial results of the systemic medication dupilumab, an inhibitor of the IL-4 receptor α subunit (which inhibits both IL-4 and IL-13 signaling), are currently being reviewed by the FDA. Semin Cutan Med Surg 36(suppl2):S45-S48 © 2017 published by Frontline Medical Communications

Keywords
Atopic dermatitis; crisaborole; eczema; dupilumab; interleukin inhibition; OPA-15406; phosphodiesterase-4 inhibition

The basic nature of atopic dermatitis (AD)—that it is the manifestation of an immune-mediated inflammatory process—has been recognized for several decades. Research has revealed that type 2 T helper cells (Th2) play an important role in this process, as does dysfunction of the skin barrier. More recently, improved understanding of the pathogenesis of AD has prompted changes in our treatment strategies and spurred the development of new therapies. This article discusses two new topical medications that target the enzyme phosphodiesterase (PDE) (crisaborole and OPA-15406), current thinking on the role of systemic agents in AD, as well as new and emerging systemic agents. In recent years, several immunologic mediators—PDE, small molecules, and Janus kinase—have been shown to be important in the course of AD, both because they have been implicated in the pathogenesis of AD and because of evidence that blocking these mediators can help change the disease process.

PDE: A Novel Target for AD Treatment
About 30 years ago, while studying leukocytes and macrophages in patients with AD and asthma, Hanifin and colleagues1 discovered that activity of the enzyme PDE was increased and cyclic adenosine monophosphate (cAMP) activity was decreased in the presence of AD signs and symptoms. In normal cells, cAMP is present in a considerable quantity, and PDE can help mediate its consumption, but in inflammatory cells, PDE is overactive, cAMP is decreased, and a generalized overexpression of a number of proinflammatory cytokines ensues.

Many years after the work by Hanifin and colleagues was published, PDE was recognized as a potential target molecule for anti-inflammatory medications. Subsequent research determined that inhibition of PDE type 4 (PDE-4) results in increased levels of intracellular cAMP, the reduction of cytokine mediator release, and mitigation of the inflammatory processes involved in AD. PDE-4 inhibiting agents—several topicals and one systemic—have been investigated for the treatment of AD. The topical agent crisaborole was recently approved by the US Food and Drug Administration (FDA) for the treatment of AD. The other topical medication, OPA-15406 (also known as MM36), and the systemic PDE-4 inhibitor apremilast (currently approved for the treatment of moderate to severe plaque psoriasis and psoriatic arthritis) are being investigated as AD therapies that target the PDE-4 pathways.

Crisaborole
A new boron-based PDE-4 inhibitor, crisaborole, was approved by the FDA in December 2016 for the treatment of AD. The incorporation of a boron ring into the cyclic structure of this agent allows effective penetration of the skin and access to target cells. In addition, the integration of boron into the molecule is thought to increase the stability of crisaborole and improve target binding and selectivity.

The safety and efficacy of crisaborole ointment 2% were evaluated in two identically designed randomized, double-blind, vehicle-controlled phase III trials—referred to as AD-301 and AD-302—involving a combined total of more than 1,500 patients with mild or moderate AD.2 The study populations (n=759 in AD-301 and n=763 in AD-302) included patients 2 years of age and older, with an average age of 12 years across both studies (range, 2-80 years). About one-third of the enrolled patients had mild AD and the rest had moderate disease, based on an Investigator's Static Global Assessment (ISGA) score. The mean affected body surface...
area (BSA) in AD-301 was 18.8% in the crisaborole group and 18.6% in the vehicle group; the mean BSA in AD-302 was 17.9% in the crisaborole group and 17.7% in the vehicle group.

The patients were assigned to receive crisaborole or vehicle in a ratio of 2:1. All subjects were instructed to apply the assigned study drug twice a day to all of the areas of AD identified at the baseline evaluation for 28 days.

The primary efficacy endpoint at day 29 was an ISGA score of clear or almost clear skin plus at least two grades of improvement over baseline. The investigators also evaluated time to success in the ISGA score, the percentage of patients who achieved a score of clear or almost clear, a decrease in the severity of AD signs, and the time to improvement in pruritus. Significantly more patients in the active-treatment groups in both AD-301 and AD-302 achieved success on the ISGA score than did the patients in the vehicle groups: in AD-301, 32.8% vs 25.4% \( (P=0.038) \) and in AD-302, 31.4% vs 18.0% \( (P<0.001) \). Improvements in the secondary endpoints also were superior in the patients in the active-treatment groups (Figure 1 and Table 1).

Treatment-emergent adverse events were reported in about 11% of patients across both studies, and included AD and pain at the application site; a small percentage of patients had application site infection.

After completion of the 28-day phase III pivotal trials, patients had the opportunity to continue treatment by enrolling in a multicenter, open-label, long-term (48-week) extension safety study. A total of 517 patients opted to enroll. Patients were assessed for severity of their AD every 4 weeks and were treated with 4-week cycles of crisaborole as needed—ie, when severity was assessed as ISGA score of 2 or more (mild).

During this open-label extension and the pivotal studies, approximately 65% of patients had at least one treatment-emergent adverse event: severity of the events was mild or moderate, with most of these considered to be unrelated to treatment. Seven serious treatment-emergent adverse events were reported in the extension study, and none of these was considered to be treatment-related.

Treatment-related adverse events included burning and stinging at the application site. No cases of application site atrophy, telangiectasia, or hypopigmentation were reported.

OPA-15406

Phase II studies have been completed on another topical PDE-4 inhibitor, OPA-15406. In a randomized, double-blind, vehicle-controlled dose-finding study, Hanifin and colleagues compared two concentrations of OPA-15406 with vehicle in 121 patients between 10 and 70 years of age: OPA-15406 0.3% \( (n=41) \), OPA-15406 1% \( (n=43) \), and vehicle \( (n=37) \). The patients applied the study medication to the AD-affected sites twice daily for 8 weeks. The primary endpoint was an Investigator’s Global Assessment (IGA) of 0 or 1, with a 2-grade reduction in AD severity at week 4. This endpoint was achieved in the OPA-15406 1% group \( (P=0.0165 \text{ vs vehicle}) \) (Figure 2A). In addition, the investigators noted that based on blood samples tested for OPA-15406, systemic absorption of this agent was negligible.

### TABLE 1  Crisaborole 2% Ointment: Summary of Phase III Studies Efficacy Results

<table>
<thead>
<tr>
<th></th>
<th>AD-301 (crisaborole/vehicle) N=503/256</th>
<th>AD-302 (crisaborole/vehicle) N=513/250</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint day 29</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% ISGA success: Score of 0 (clear) or 1 (almost clear) with ≥2-grade improvement</td>
<td>32.8%/25.4% ( (P=0.038) )</td>
<td>31.4%/18% ( (P&lt;0.001) )</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISGA of clear or almost clear (0 or 1)</td>
<td>51.7%/40.6% ( (P=0.005) )</td>
<td>48.5%/29.7% ( (P&lt;0.001) )</td>
</tr>
<tr>
<td><strong>Time to success in ISGA:</strong> Crisaborole achieved success earlier than vehicle-treated patients ( (P&lt;0.001) ).</td>
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</table>

ISGA=Investigator’s Static Global Assessment.

Systemic Therapy
The use of systemic treatments in children with AD whose disease is not adequately controlled with nonpharmacologic and topical treatments varies considerably among practitioners. This lack of treatment standardization is the result of insufficient evidence from clinical studies because pediatric patients are often excluded from enrollment. Two studies—one from the European Dermato-Epidemiology Network (EDEN) in Europe and the other from the Pediatric Dermatology Research Alliance (PeDRA) in the United States and Canada—surveyed clinicians to determine which of the currently available systemic medications they use in pediatric patients, and under what circumstances.

The European TREATment of Severe Atopic Eczema in Children Taskforce (TREAT) survey, conducted by EDEN, examined prescribing practices using currently available systemic agents. Among the 343 respondents (89.2% of whom were dermatologists), 71% said they use systemic immunosuppression for children with severe AD. The first-line agents of choice were cyclosporine (43.0%), oral corticosteroids (30.7%), and azathioprine (21.7%). The second-line agent of choice was cyclosporine (33.6%), and the third-line choice was methotrexate (26.2%).

In the United States and Canada, 133 members of the Society for Pediatric Dermatology responded to PeDRA’s TREAT survey. In addition to determining prescribing practices, this survey sought to identify factors that discouraged the use of systemic agents. The survey showed that 113 respondents (86.5%) said they use systemic therapy for severe AD in pediatric patients. The preferred first-line agents were cyclosporine (45.2%), methotrexate (29.6%), and mycophenolate mofetil (30.4%). Methotrexate (13.0%) and mycophenolate mofetil (30.4%) were the preferred second-line agents, and azathioprine was the most commonly used third-line agent. Two factors were most commonly cited as issues that discouraged the use of systemic agents in pediatric patients: side effect profiles (82.6%) and suspected risk for long-term toxicity (81.7%).

At a crucial hearing of an FDA Advisory Committee on pediatric adverse events, eight professional societies, including PeDRA, the American Academy of Dermatology, and the Society for Pediatric Dermatology, endorsed a statement of advocacy regarding the need for studies of systemic agents in children with AD.

A number of new systemic agents currently are being investigated for the treatment of AD. Phase III studies on adult patients with AD have been completed on one of these agents, dupilumab, which is discussed below. Other systemic agents that target a variety of pathogenetic pathways (Table 2) are being evaluated in or have completed phase II clinical studies.

Dupilumab
A new systemic agent, dupilumab, is an inhibitor of the interleukin (IL)-4 receptor α subunit, which results in inhibition of both IL-4 and IL-13 signaling. Two identically designed phase III, 16-week trials of dupilumab monotherapy (SOLO 1 and SOLO 2) in adult patients with mild to moderate AD have been completed, and the results have been published.

The studies involved 1,379 patients, 18 years of age and older, whose AD was not adequately controlled with topical agents or who were not candidates for topical medication. To be eligible for enrollment, patients were required to have a score of 3 or 4 on the IGA scale. Patients were also assessed at baseline using the Eczema Area and Severity Index (EASI) and other measures of AD, although defined scores on these evaluations were not required for enrollment. Patients were randomized to three active-treatment arms or to a placebo group. The active-treatment groups received dupilumab, 300 mg once weekly; dupilumab, 300 mg every 2 weeks; or an initial loading dose of 600 mg of dupilumab, followed by placebo for 16 weeks. The primary endpoint was the proportion of patients who had a score of 0 or 1 (clear or almost clear) in the IGA plus a reduction from baseline IGA of at least 2 points.

In the 300 mg/week dupilumab groups in SOLO 1 and SOLO 2, 37% and 36% of patients, respectively, achieved the endpoint IGA scores of clear or almost clear. In the groups

![FIGURE 2 OPA-15406 Phase II Study Efficacy Data](image)

**A.** Mean success rates per visit defined as an Investigator’s Global Assessment (IGA) score of 0 or 1 with ≥2-grade change.

**B.** Mean rates of an IGA score of 0 or 1.

**TABLE 2 Systemic Agents for Atopic Dermatitis in Ongoing or Completed Phase II Trials**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE-4 inhibitor (oral)</td>
<td>Apremilast (oral)</td>
</tr>
<tr>
<td>IL-13 inhibitors</td>
<td>Lebrikizumab</td>
</tr>
<tr>
<td>IL-31 inhibitor</td>
<td>Nemolizumab</td>
</tr>
<tr>
<td>JAK inhibitors</td>
<td>Tofacitinib</td>
</tr>
<tr>
<td>Antileukotriene agents</td>
<td>Q301</td>
</tr>
<tr>
<td>H4 blockers</td>
<td>QAW039</td>
</tr>
<tr>
<td>Liver X receptor antagons</td>
<td></td>
</tr>
</tbody>
</table>

*H=histamine; IL=interleukin; JAK=Janus kinase; PDE-4=phosphodiesterase type 4.*
who received 300 mg every 2 weeks, 38% and 36%, respectively, achieved scores of clear or almost clear. By comparison, 10.3% and 8.5% of patients in the placebo groups in SOLO 1 and SOLO 2, respectively, had IGA scores of clear or almost clear. The differences in achievement of the primary endpoint were significantly different in all treatment-group vs placebo-group comparisons ($P<0.0001$ for all comparisons).

In the treatment groups who received 300 mg/week dupilumab, improvements at week 16 over baseline in EASI scores were 72% and 69% in SOLO 1 and SOLO 2, respectively. In the patients who received 300 mg dupilumab every 2 weeks, EASI improvements were 72% and 67%, respectively, in SOLO 1 and SOLO 2. In the placebo groups, EASI improvements over baseline were 38% and 31% (the treatment-group vs placebo-group comparisons were statistically significant, at $P<0.0001$ for all comparisons).

Improvements of at least 75% in the EASI score (EASI 75) were seen in 52.5% and 48% of the groups who received 300 mg/week dupilumab in SOLO 1 and SOLO 2, respectively. EASI 75 was achieved by 51% and 44% of patients who received 300 mg dupilumab every 2 weeks in SOLO 1 and SOLO 2, respectively. In the placebo groups, 15% and 12% of patients achieved EASI 75 (comparisons with both treatment groups were statistically significant, $P<0.0001$). These 16-week efficacy results are summarized in Figure 3.

Adverse events occurred during the treatment period in 65% of patients in the dupilumab treatment groups in SOLO 1 and in 73% of patients in SOLO 2, vs 65% and 73% of patients in the corresponding placebo groups, respectively. Serious adverse events were seen in 1% and 3% of patients in the SOLO 1 and SOLO 2 dupilumab treatment groups, respectively, and in 5% and 6% in the corresponding placebo groups. The most commonly reported adverse events in the treatment group were injection site reactions and conjunctivitis. No patients dropped out of the study because of an injection site reaction; one patient discontinued because of conjunctivitis.

A long-term (120 weeks), phase III, open-label extension study of dupilumab in pediatric patients with AD is currently recruiting subjects. The primary objective of the study is to assess the long-term safety of dupilumab in this population. The secondary objectives are to assess the long-term efficacy of the medication in pediatric patients with AD, and to assess the trough concentrations of dupilumab in serum, as well as immunogenicity in this population after re-treatment with dupilumab. To be eligible, patients must be at least 6 years of age and younger than 18 years at the time of screening. In addition, patients must have participated in a previous phase II dupilumab study in patients with AD and satisfactorily completed the visits and assessments required in the previous study’s protocol.

The primary endpoint is the incidence and rate of treatment-emergent adverse events from baseline to week 120 (the last study visit). Secondary outcome measures are the incidence and rate (events per patient-year) of serious adverse events and adverse events of special interest throughout the study period; the proportion of patients who achieve and maintain remission; the proportion of patients who achieve and maintain EASI 75 or better during the study; and the proportion of patients who achieve and maintain at least a 50% reduction in EASI (EASI 50) during the study.

**Conclusion**

Evolving understanding of the pathogenesis of AD, combined with the crucial clinical need for improved therapy, has created a fertile environment for drug discovery and development. New topical and systemic agents hold promise as important advances in AD management.

**References**

1. The characteristic, age-related anatomic distribution of atopic dermatitis in adolescents and adults includes the:
   A. Antecubital fossa
   B. Face (especially the cheeks and chin)
   C. Neck
   D. Popliteal fossa

2. Which of the following is a rare condition in the differential diagnosis of atopic dermatitis?
   A. Acrodermatitis enteropathica
   B. Contact dermatitis
   C. Keratosis pilaris
   D. Nummular dermatitis

3. In adults, the occurrence of __________ should prompt consideration of other conditions in the differential diagnosis of atopic dermatitis.
   A. Hand dermatitis
   B. Late-onset signs and symptoms of atopic dermatitis
   C. Pruritus
   D. Wrist and ankle involvement

4. According to a study by Wen and colleagues, about 70% of patients with atopic dermatitis have a positive family history for __________.
   A. Atopic diseases
   B. Gluten sensitivity
   C. Peanut allergy
   D. Seborrheic dermatitis in infancy

5. One strategy that may prevent atopic dermatitis in babies is regular use of __________ starting at birth.
   A. Antibacterial soaps
   B. Bleach baths
   C. Crisaborole
   D. Emollients

6. One of the three main factors involved in the risk for persistence of atopic dermatitis into adulthood, identified recently by Kim and colleagues, is:
   A. Disease in childhood that persists for up to 5 years
   B. Greater compared to less severity of atopic dermatitis in childhood
   C. Onset of disease earlier than 2 years of age
   D. Resistance to topical calcineurin inhibitors

7. Evidence regarding bleach baths shows that they __________.
   A. Dry the skin when used more than twice weekly
   B. Have both anti-inflammatory and anti-infective properties
   C. Should be used according to standards set by the American Academy of Dermatology
   D. Should not be used when skin is severely inflamed

8. The American Academy of Dermatology Guidelines for the treatment of atopic dermatitis recommend proactive use of topical __________ as maintenance for relapse prevention, with intermittent periods of applications twice or three times weekly on areas that commonly flare.
   A. Antimicrobial creams or ointments
   B. Calcineurin inhibitors
   C. Emollients
   D. Interleukin inhibitors

9. Two new nonsteroidal topical agents, crisaborole (recently approved by the US Food and Drug Administration) and OPA-15406 (currently in clinical trials) for the treatment of atopic dermatitis target __________.
   A. Interleukin-13
   B. Phosphodiesterase type 4
   C. Tumor necrosis factor-α
   D. Type 2 T helper cells

10. __________ is a novel systemic agent for the treatment of atopic dermatitis that targets the interleukin (IL)-4 receptor α subunit.
    A. Dupilumab
    B. Lebrikizumab
    C. OPA-15406
    D. Tofacitinib
Meeting the Challenge of Atopic Dermatitis From Infancy to Adulthood Evaluation Form

Original Release Date: April 2017  •  Expiration Date: March 31, 2019  •  Estimated Time to Complete Activity: 2.0 hours

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- [ ] MSN/BSN/RN
- [ ] PA
- [ ] APN/NP
- [ ] PharmD/RPh
- [ ] Resident/Fellow Researcher
- [ ] Administrator
- [ ] Student
- [ ] Other; specify ____________________________

**LEARNING OBJECTIVES** Having completed this activity, you are better able to:

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Somewhat Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discuss the features of atopic dermatitis (AD) that should allow a clinical diagnosis of the condition in most patients, and list the factors in children and adults that should lead to the consideration of alternative diagnoses or identification of comorbid conditions.</td>
<td>[ ] 5</td>
<td>[ ] 4</td>
<td>[ ] 3</td>
<td>[ ] 2</td>
</tr>
<tr>
<td>Explain how the current understanding of the role of the epidermal skin barrier and transepidermal water loss should affect—and continue to improve—the day-to-day care of patients with AD.</td>
<td>[ ] 5</td>
<td>[ ] 4</td>
<td>[ ] 3</td>
<td>[ ] 2</td>
</tr>
<tr>
<td>More effectively individualize patient treatment strategies by considering the full range of current and emerging therapeutic options.</td>
<td>[ ] 5</td>
<td>[ ] 4</td>
<td>[ ] 3</td>
<td>[ ] 2</td>
</tr>
<tr>
<td>Consider the evidence-based recommendations in the current guidelines for the diagnosis and treatment of AD published by the American Academy of Dermatology.</td>
<td>[ ] 5</td>
<td>[ ] 4</td>
<td>[ ] 3</td>
<td>[ ] 2</td>
</tr>
<tr>
<td>Describe the rationales and mechanisms of action of the new and emerging therapies for AD, particularly the recently approved topical agent crisaborole and the systemic medication dupilumab (phase III study results under FDA review at the time of publication of this supplement).</td>
<td>[ ] 5</td>
<td>[ ] 4</td>
<td>[ ] 3</td>
<td>[ ] 2</td>
</tr>
</tbody>
</table>

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

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**

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Somewhat Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>The information presented increased my awareness/understanding of the subject.</td>
<td>[ ] 5</td>
<td>[ ] 4</td>
<td>[ ] 3</td>
<td>[ ] 2</td>
</tr>
<tr>
<td>The information presented will influence how I practice/do my job.</td>
<td>[ ] 5</td>
<td>[ ] 4</td>
<td>[ ] 3</td>
<td>[ ] 2</td>
</tr>
<tr>
<td>The information presented will help me improve patient care/my job performance.</td>
<td>[ ] 5</td>
<td>[ ] 4</td>
<td>[ ] 3</td>
<td>[ ] 2</td>
</tr>
<tr>
<td>The program was educationally sound and scientifically balanced.</td>
<td>[ ] 5</td>
<td>[ ] 4</td>
<td>[ ] 3</td>
<td>[ ] 2</td>
</tr>
<tr>
<td>Overall, the program met my expectations.</td>
<td>[ ] 5</td>
<td>[ ] 4</td>
<td>[ ] 3</td>
<td>[ ] 2</td>
</tr>
<tr>
<td>I would recommend this program to my colleagues.</td>
<td>[ ] 5</td>
<td>[ ] 4</td>
<td>[ ] 3</td>
<td>[ ] 2</td>
</tr>
</tbody>
</table>

Lawrence F. Eichenfield, MD
- Author demonstrated current knowledge of the topic.
- Author was organized in the written materials.

Linda F. Stein Gold, MD
- Author demonstrated current knowledge of the topic.
- Author was organized in the written materials.

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.

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.

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