

FROM THE ACADEMY

Guidelines of care for the management of atopic dermatitis

Section 1. Diagnosis and assessment of atopic dermatitis

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Atopic dermatitis (AD) is a chronic, pruritic, inflammatory dermatosis that affects up to 25% of children and 2% to 3% of adults. This guideline addresses important clinical questions that arise in the management and care of AD, providing updated and expanded recommendations based on the available evidence. In this first of 4 sections, methods for the diagnosis and monitoring of disease, outcomes measures for assessment, and common clinical associations that affect patients with AD are discussed. Known risk factors for the development of disease are also reviewed. (J Am Acad Dermatol 10.1016/j.jaad.2013.10.010.)

Key words: assessment scales; atopic dermatitis; biomarkers; clinical associations; criteria; diagnosis; risk factors.

DISCLAIMER

Adherence to these guidelines will not ensure successful treatment in every situation. In addition, these guidelines should not be interpreted as setting a standard of care, or be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment

regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient and the known variability and biologic behavior of the disease. This guideline reflects the best available data at the time the guideline was prepared. The results of future

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Abbreviations used:

AAD:	American Academy of Dermatology
AD:	atopic dermatitis
ADHD:	attention deficit hyperactivity disorder
CDLQI:	Children's Dermatology Life Quality Index
DFI:	Dermatitis Family Impact
DLQI:	Dermatology Life Quality Index
EASI:	Eczema Area and Severity Index
FLG:	filaggrin
GREAT:	Global Resource for Eczema Trials
IGA:	Investigator's Global Assessment
IgE:	immunoglobulin E
IL:	interleukin
ISAAC:	International Study of Asthma and Allergies in Childhood
MDC:	macrophage-derived chemoattractant
POEM:	Patient-Oriented Eczema Measure
SASSAD:	Six Area, Six Sign Atopic Dermatitis
SCORAD:	SCORing Atopic Dermatitis
SORT:	strength of recommendation taxonomy
TARC:	thymus and activation-regulated chemokine
TISS:	Three-Item Severity Scale
UK:	United Kingdom

studies may require revisions to the recommendations in this guideline to reflect new data.

SCOPE

This guideline addresses the diagnosis and assessment of pediatric and adult atopic dermatitis (AD; atopic eczema) of all severities. Other forms of dermatitis, such as irritant dermatitis and allergic contact dermatitis in those without AD, are outside of the scope of this document. Recommendations on AD treatment and management are subdivided into 4 sections given the significant breadth of the topic and to update and expand on the clinical information and recommendations previously published in 2004. This document is the first section in the series and covers methods for diagnosis and monitoring of AD, disease severity and quality of life scales for outcomes measurement, and common clinical associations that affect patients. A discussion on known risk factors for the development of AD is also presented. The second guideline in the series will address the management and treatment of AD with pharmacologic and nonpharmacologic topical modalities; the third section will cover phototherapy and systemic treatment options; and the fourth section will address the minimization of disease flares, educational interventions, and use of adjunctive approaches.

METHOD

A work group of recognized AD experts was convened to determine the audience and scope of the guideline, and to identify important clinical questions in the diagnosis and assessment of AD (Table 1). Work group members completed a

disclosure of interests that was updated and reviewed for potential relevant conflicts of interest throughout guideline development. If a potential conflict was noted, the work group member recused him or herself from discussion and drafting of recommendations pertinent to the topic area of the disclosed interest.

An evidence-based model was used and evidence was obtained using a systematic search of PubMed, the Cochrane Library, and the Global Resource for Eczema Trials (GREAT)¹ databases from November 2003 through November 2012 for clinical questions addressed in the previous version of this guideline published in 2004, and from 1964 to 2012 for all newly identified clinical questions as determined by the work group to be of importance to clinical care. Searches were prospectively limited to publications in the English language. MeSH terms used in various combinations in the literature search included: atopic dermatitis, atopic eczema, diagnosis, diagnostic, severity course, assessment, biomarkers, outcomes measures, morbidity, quality of life, appearance, comorbidity, food allergy, allergic rhinitis, asthma, cancer, sleep, growth effects, developmental effects, behavioral, psychological, attention deficit hyperactivity disorder (ADHD), treatment, and outcome. A total of 1417 abstracts were initially assessed for possible inclusion. After removal of duplicate data, 292 were retained for final review based on relevancy and the highest level of available evidence for the outlined clinical questions. Evidence tables were generated for these studies and used by the work group in developing recommendations. The Academy's previously published guidelines on AD were also evaluated, as were other current published guidelines on AD.²⁻⁵

The available evidence was evaluated using a unified system called the Strength of Recommendation Taxonomy (SORT) developed by editors of US family medicine and primary care journals (ie, *American Family Physician*, *Family Medicine*, *Journal of Family Practice*, and *BMJ USA*).⁶ Evidence was graded using a 3-point scale based on the quality of study methodology (eg, randomized control trial, case control, prospective/retrospective cohort, case series, etc) and the overall focus of the study (ie, diagnosis, treatment/prevention/screening, or prognosis) as follows:

- I. Good-quality patient-oriented evidence (ie, evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life).
- II. Limited-quality patient-oriented evidence.
- III. Other evidence, including consensus guidelines, opinion, case studies, or disease-oriented evidence (ie, evidence measuring intermediate, physiologic,

Table I. Clinical questions used to structure the evidence review for the diagnosis and assessment of atopic dermatitis

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- What are the most valid and reliable methods for diagnosing atopic dermatitis?*
 - What are the most useful tools to assess the severity and course of atopic dermatitis?*
 - What are the patient- and disease-specific outcome measures used to determine the relative effectiveness of a given treatment for atopic dermatitis?*
 - What common clinical associations may affect patients with atopic dermatitis?*
 - What are the epidemiologic risk factors associated with atopic dermatitis?*
-

*Indicates new clinical questions.

or surrogate end points that may or may not reflect improvements in patient outcomes).

Clinical recommendations were developed based on the best available evidence. These are ranked as follows:

- A. Recommendation based on consistent and good-quality patient-oriented evidence.
- B. Recommendation based on inconsistent or limited-quality patient-oriented evidence.
- C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence.

In situations where documented evidence-based data are not available, we have used expert opinion to generate our clinical recommendations.

This guideline has been developed in accordance with the American Academy of Dermatology (AAD)/AAD Association *Administrative Regulations for Evidence-based Clinical Practice Guidelines* (version approved May 2010), which includes the opportunity for review and comment by the entire AAD membership and final review and approval by the AAD Board of Directors.⁷ This guideline will be considered current for a period of 5 years from the date of publication, unless reaffirmed, updated, or retired at or before that time.

DEFINITION

AD is a chronic, pruritic inflammatory skin disease that occurs most frequently in children, but also affects many adults. It follows a relapsing course. AD is often associated with elevated serum immunoglobulin (IgE) levels and a personal or family history of type I allergies, allergic rhinitis, and asthma. Atopic eczema is synonymous with AD.

INTRODUCTION

AD onset is most common between 3 and 6 months of age, with approximately 60% of patients

developing the eruption in the first year of life and 90% by 5 years of age.^{8,9} While the majority of affected individuals have resolution of disease by adulthood, 10% to 30% do not, and a smaller percentage first develop symptoms as adults.¹⁰ AD has a complex pathogenesis involving genetic, immunologic, and environmental factors that lead to a dysfunctional skin barrier and dysregulation of the immune system. Notable clinical findings include erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and lichenification, but these vary by patient age and chronicity of lesions. Pruritus is a hallmark of the condition that is responsible for much of the disease burden borne by patients and their families.

DIAGNOSIS

The diagnosis of AD is made clinically and is based on historical features, morphology and distribution of skin lesions, and associated clinical signs. Formal sets of criteria have been developed by various groups to aid in classification.

One of the earliest and most recognized sets of diagnostic criteria is the 1980 Hanifin and Rajka criteria,¹¹ which requires that 3 of 4 major criteria and 3 of 23 minor criteria be met. While comprehensive and often used in clinical trials, such a large number of criteria are unwieldy for use in clinical practice. Some of the minor criteria have been noted to be poorly defined or nonspecific, such as pityriasis alba, while others, such as upper lip cheilitis and nipple eczema, are quite specific for AD but uncommon.^{11,12} Several international groups have proposed modifications to address these limitations (eg, Kang and Tian criteria, International Study of Asthma and Allergies in Childhood [ISAAC] criteria).¹³⁻¹⁶ The United Kingdom (UK) Working Party, in particular, systematically distilled the Hanifin and Rajka criteria down to a core set that is suitable for epidemiologic/population-based studies and that can be used by nondermatologists. These consist of 1 mandatory and 5 major criteria and do not require any laboratory testing. Both the Hanifin and Rajka and UK Working Party diagnostic schemes have been validated in studies and tested in several different populations.^{12,13,15,17-23}

A 2003 consensus conference spearheaded by the American Academy of Dermatology suggested revised Hanifin and Rajka criteria that are more streamlined and additionally applicable to the full range of ages affected.²⁴ While this set has not been assessed in validation studies, it is felt by the current work group that an adaptation of this pragmatic approach for diagnosing AD in infants, children, and adults is well suited for use in the clinical setting

Box 1. Features to be considered in the diagnosis of patients with atopic dermatitis**ESSENTIAL FEATURES**—Must be present:

- Pruritus
- Eczema (acute, subacute, chronic)
 - Typical morphology and age-specific patterns*
 - Chronic or relapsing history

**Patterns include:*

1. Facial, neck, and extensor involvement in infants and children
2. Current or previous flexural lesions in any age group
3. Sparing of the groin and axillary regions

IMPORTANT FEATURES—Seen in most cases, adding support to the diagnosis:

- Early age of onset
- Atopy
 - Personal and/or family history
 - Immunoglobulin E reactivity
- Xerosis

ASSOCIATED FEATURES—These clinical associations help to suggest the diagnosis of atopic dermatitis but are too nonspecific to be used for defining or detecting atopic dermatitis for research and epidemiologic studies:

- Atypical vascular responses (eg, facial pallor, white dermographism, delayed blanch response)
- Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis
- Ocular/periorbital changes
- Other regional findings (eg, perioral changes/periauricular lesions)
- Perifollicular accentuation/lichenification/prurigo lesions

EXCLUSIONARY CONDITIONS—It should be noted that a diagnosis of atopic dermatitis depends on excluding conditions, such as:

- Scabies
- Seborrheic dermatitis
- Contact dermatitis (irritant or allergic)
- Ichthyoses
- Cutaneous T-cell lymphoma
- Psoriasis
- Photosensitivity dermatoses
- Immune deficiency diseases
- Erythroderma of other causes

Adapted from Eichenfield et al.²⁴ Used with permission of the American Academy of Dermatology.

(Box 1). The original UK criteria cannot be applied to very young children, although revisions to include infants have since been proposed.²⁵⁻²⁷

The recommendation for the diagnosis of AD is shown in Table II, and the strength of the recommendation is displayed in Table III. AD should be differentiated from other red, scaly skin conditions. It is often difficult to separate AD from seborrheic dermatitis in infancy, and the 2 conditions may overlap in this age group. AD usually spares the groin and axillary

regions, while seborrheic dermatitis affects these areas and tends not to be pruritic. Particularly if not responding to therapy, the diagnosis of AD should be re-reviewed and other disorders considered, including more serious nutritional, metabolic, and immunologic conditions in children and cutaneous T-cell lymphoma in adults. Allergic contact dermatitis may be both an alternative diagnosis to AD and/or an exacerbator of AD in some individuals (further discussed in section 4 of the guideline series).

Table II. Recommendation for the diagnosis of atopic dermatitis

Patients with presumed atopic dermatitis should have their diagnosis based on the criteria summarized in [Box 1](#). On occasion, skin biopsy specimens or other tests (such as serum immunoglobulin E, potassium hydroxide preparation, patch testing, and/or genetic testing) may be helpful to rule out other or associated skin conditions.

BIOMARKERS

The diagnosis of AD remains clinical, because there is currently no reliable biomarker that can distinguish the disease from other entities. The most commonly associated laboratory feature, an elevated total and/or allergen-specific serum IgE level, is not present in about 20% of affected individuals.²⁸ Some denote “extrinsic” and “intrinsic” groups of disease based on the presence or absence of IgE elevation, but whether these are true variants remains controversial. Some individuals will later develop elevated IgE levels, and recent knowledge of skin barrier defects and studies on epicutaneous sensitization suggest that elevated IgE may be a secondary phenomenon.²⁸ Elevated allergen-specific IgE levels are also nonspecific, because they are found in 55% of the US general population.²⁹ Although the total IgE level does tend to vary with disease severity, it is not a reliable indicator, because some individuals with severe disease have normal values, and IgE may also be elevated in multiple nonatopic conditions (eg, parasitic infection and certain cancers and autoimmune diseases).^{28,30,31} Increases in tissue mast cells and peripheral eosinophil counts have also been evaluated, but with similar inconsistent association.^{30,32-34}

Discovery of new T-lymphocyte subsets and novel cytokines and chemokines have generated a myriad of additional potential biomarkers. These include serum levels of CD30, macrophage-derived chemoattractant (MDC), interleukins (IL)-12, -16, -18, and -31, and thymus and activation-regulated chemokine (TARC). Some have shown a correlation with AD disease severity using the SCORing Atopic Dermatitis (SCORAD) index and other severity scales.³⁵⁻⁴⁰ But to date, none have shown reliable sensitivity or specificity for AD to support general clinical use for diagnosis or monitoring. Most studies suffer from a small cohort size and involve selection from tertiary care centers with more severe disease rather than from general populations. Few have compared levels in AD with that in other eczematous conditions or other atopic conditions to assess whether the biomarker is a specific indicator for AD.

Markers for prognosis are also inconsistent, although high total serum IgE levels and filaggrin (*FLG*) gene null mutations do tend to predict a more severe and protracted course of disease (discussed further below in “Risk factors for disease development”).^{9,28,41,42} Recommendations for the use of biomarkers in the assessment of AD are shown in [Table IV](#), and the strength of the recommendations are summarized in [Table III](#).

DISEASE SEVERITY AND CLINICAL OUTCOMES ASSESSMENT**Disease severity scales**

For the measurement of disease severity, 28 different scales were identified, without a single gold standard emerging.⁴³⁻⁵⁶ They use various methods that include grid patterns and objective disease features and extent, and some scales incorporate subjective disease features. The most commonly used disease severity scales are the SCORAD index, the Eczema Area and Severity Index (EASI), Investigator’s Global Assessment (IGA), and the Six Area, Six Sign Atopic Dermatitis (SASSAD) severity score.⁴³ These scales are primarily used in clinical trials and rarely in clinical practice, as they were generally not designed for this purpose.

Scale development in many cases included rigorous testing and evaluation of the following statistical properties: inter- and intrarater reliability, validity (ie, construct, content, and concurrent), internal consistency reliability, responsiveness to change, and minimal clinically important difference.^{44,45} The available literature suggests that the SCORAD index, the EASI score, and the Patient-Oriented Eczema Measure (POEM) severity scale have been adequately tested and validated; therefore, their use can be considered when practical.⁴⁴ Of note, the EASI uses objective physician estimates of disease extent and severity, while SCORAD incorporates both objective physician estimates of extent and severity and subjective patient assessment of itch and sleep loss.⁵⁰ POEM was specifically designed to measure severity from the patient perspective and uses 7 questions regarding symptoms and their frequency.⁴³ The Three Item Severity Scale (TISS) is another simplified scale that shows promise for future use in clinical practice, but it needs additional testing.^{44,54}

Recognizing the lack of uniformity in disease-severity scale use, international efforts are underway to standardize measured outcomes.⁵⁷ This includes development of a core set of valid measures of signs and symptoms that can be feasibly recorded in controlled trials, which is directed toward

Table III. Strength of recommendations for the diagnosis and assessment of atopic dermatitis

Recommendation	Strength of recommendation	Level of evidence	References
Diagnosis made using criteria in Box 1	C	III	12,13,15-23,146-149
No specific biomarkers for diagnosis or severity assessment	B	II	30-40,150-164
Immunoglobulin E levels not routinely recommended	A	I	5,30,31,34,35,165,166
Available disease severity scales not for routine clinical use	C	II	44,45,48,49,54,66,67,167-176
Available quality of life severity scales not for routine clinical use	C	II	58,60,67,68
Should query itch, sleep, impact on daily activity, and disease persistence	C	III	69-76
Awareness and discussion of common associations	C	I and II	69,70,77-84,92-98,103,104
Integrated, multidisciplinary approach to care	C	III	107,108

Table IV. Recommendations for the use of biomarkers in the assessment of atopic dermatitis

For patients with presumed atopic dermatitis, there are no specific biomarkers that can be recommended for diagnosis and/or assessment of disease severity.

Monitoring of immunoglobulin E levels is not recommended for the routine assessment of disease severity.

improving comparisons across trials and facilitating metaanalyses.

Quality of life scales and disease impact measurements

Twenty-two different AD-specific, dermatology-specific, and generic scales were identified that measure quality of life and other psychological outcomes in patients with AD.^{43,58-66} These scales have been used to assess the impact of AD and the effects of interventions, as well as to make comparisons with the impact of other disorders. Careful consideration of the scale properties should occur before use, including validity (ie, content, construct, concurrent, and discriminative), reliability (ie, test-retest and internal consistency), responsiveness to change, and minimal clinically important difference.^{58,60,67,68} In clinical trials, the most commonly used scale is the Children's Dermatology Life Quality Index (CDLQI), followed by the Dermatitis Family Impact (DFI), the Dermatology Life Quality Index (DLQI), and the Infant's Dermatology Life Quality Index,⁴³ but these scales were not generally designed for use in routine clinical practice.⁶⁹

Additional development and evaluation of practical clinical quality of life scales are needed. This could be done by modifying existing scales into short clinical versions or by testing existing scales in a clinic population. Of note, the inclusion of patient assessment of pruritus is critical given its central contribution to the morbidity of AD.^{70,71} Ratings of

itch intensity, whether made by parents for young children or by older individuals for themselves, significantly and inversely correlate with quality of life.^{72,73} The difficulties associated with itching and the resultant scratching are typically the first to be mentioned by parents when asked about the effects of their child's disease.⁷⁴ The mechanisms underlying AD-associated itch remain unclear, and are an area of much active research. Sleep disturbance, the impedance of daily activities (including effects on work or school performance), and persistence of disease are other key measures of disease impact, and represent a patient's status and overall well-being.^{69,75,76} Recommendations on assessment are summarized in [Table V](#) and the strength of recommendations in [Table III](#).

CLINICAL ASSOCIATIONS

Common associations/comorbidities of AD that have been supported by studies include other atopic conditions, namely food allergies, asthma, and allergic rhinitis/rhinoconjunctivitis.⁷⁷⁻⁸⁴ Some consider AD to be the start of the "atopic march," given the frequent subsequent development of one or more of the other atopic conditions. However, the association of other atopic conditions with AD is complex and multifactorial, because this progression does not happen in all individuals. Patients living in humid climates or developing countries may manifest AD only after changing their locale and/or after the onset of respiratory allergies.⁸⁵⁻⁸⁸

Sleep disturbance is also common and stems in large part from the significant itch associated with AD.^{69,70,89,90} Sleep is disrupted in up to 60% of children with eczema, increasing to 83% during exacerbation.⁹¹ Along with the affected individual, other family members may also suffer as a result of being awakened.⁶⁸ Even when in clinical remission, individuals with eczema have more sleep disturbance than do healthy individuals.⁹¹ Greater skin disease severity also appears to have an effect

Table V. Recommendations for disease severity and clinical outcomes assessment

For the general management of patients with atopic dermatitis, available disease severity measurement scales are not recommended for routine clinical practice, because they were not usually designed for this purpose.

For the general management of patients with atopic dermatitis, available patient quality of life measurement scales are not recommended for routine clinical practice.

It is recommended that clinicians ask general questions about itch, sleep, impact on daily activity, and persistence of disease, and currently available scales be used mainly when practical.

on mood. Depression has been noted in both teens and adults affected with AD.^{92,93} More recently, there has been a suggested association of AD with behavior disorders, including ADHD, especially in children.^{94,95} However, an association does not establish causality, and the precise nature of the relationship requires additional study, including the role of sleep disturbance and ADHD-like behaviors and the possibility of nonspecific linkage to any chronic disease of childhood.⁹⁴

Cancer and obesity have been inconsistently associated with AD. There does not appear to be an increased risk of skin cancer or of internal malignancies, although some data are suggestive of higher rates of lymphoma and lower rates of glioma.⁹⁶⁻¹⁰⁰ At present, there are insufficient data to warrant special screening or caution. AD has been linked to obesity in a few epidemiologic studies.^{101,102} However, short stature and poor growth have also been documented, particularly in children who suffer from severe skin disease.¹⁰³⁻¹⁰⁶

The recommendations regarding the assessment for clinical associations of AD (Table VI) are based on group consensus, because there is no high-quality, conclusive evidence to show that screening for them leads to improved patient outcomes. The benefits of taking an integrated, multidisciplinary clinical approach to the care of AD patients with common associations are mainly limited to a few case reports.^{107,108} Eczema schools and other educational programs will be discussed in section 4 of the guidelines.

RISK FACTORS FOR DISEASE DEVELOPMENT

Two risk factors appear to be consistently and strongly associated with the development of AD: (1) a family history of atopy and (2) the loss of function mutations in the *FLG* gene.

Table VI. Recommendations for the assessment of clinical associations of atopic dermatitis

Physicians should be aware of and assess for conditions associated with atopic dermatitis, such as rhinitis/rhinoconjunctivitis, asthma, food allergy, sleep disturbance, depression, and other neuropsychiatric conditions, and it is recommended that physicians discuss them with the patient as part of the treatment/management plan, when appropriate.

An integrated, multidisciplinary approach to care may be valuable and is suggested for atopic dermatitis patients who present with common associations.

Approximately 70% of AD patients have a positive family history of atopic diseases.¹⁰⁹ The odds of developing AD are 2- to 3-fold higher in children with 1 atopic parent, and this increases to 3- to 5-fold if both parents are atopic.^{110,111} A maternal history of AD is possibly more predictive.¹¹² The *FLG* gene encodes profilaggrin, which is degraded to filaggrin monomers, and these proteins play key roles in the terminal differentiation of the epidermis and formation of the skin barrier, including the stratum corneum. Filaggrin breakdown products are part of natural moisturizing factor, which contributes to epidermal hydration and barrier function. *FLG* null mutations confer a risk for earlier-onset AD, and for more severe, persistent disease.^{113,114} They also lead to an increased tendency for eczema herpeticum. Different defects in *FLG* have been noted in different ethnic populations with AD, showing its importance to pathogenesis. However, a significant number of patients with AD have no known *FLG* mutations, and conversely, approximately 40% of individuals with *FLG* null alleles do not develop AD.¹¹³

The type of delivery during childbirth (ie, caesarean or vaginal) does not appear to alter AD risk.¹¹⁵ Elevated birth weights may be a risk factor for disease development, but the effect size is likely small because studies have been conflicting, with some showing a negative association.¹¹⁶⁻¹¹⁸

While patients with AD are often sensitized to certain foods, the timing of solid food introduction or withholding of allergenic foods does not appear to alter the risk for AD.¹¹⁹ Most studies of dietary modification of the maternal or infant diet do not show a protective effect, although recently published studies of hydrolyzed formula and probiotic supplementation suggest that these approaches could have a beneficial effect in preventing disease development in some high-risk infants who are not exclusively breast fed.¹²⁰⁻¹²⁵ At present, however, there is insufficient evidence to recommend any specific dietary or other measures as being effective

for the primary prevention of AD. Breastfeeding for the first 6 months of life is encouraged for its other benefits for the infant and mother (eg, bonding and passive immunity).

There are no consistent findings to suggest that male or female sex affects AD risk, but being of black race does appear to increase risk.¹²⁶ A higher level of parental education is a risk factor for disease, but the effect of socioeconomic status is unclear.^{126,127} Previous studies found a higher risk of AD in higher socioeconomic groups, but more recent studies failed to confirm these findings.^{128,129} Living in urban areas appears likely to increase the risk of AD, but studies attempting to identify causative environmental agents have not been conclusive.¹³⁰ Daycare may influence the risk of AD development, but studies that offer better control for confounders are needed before additional conclusions can be made.^{126,131}

The effect of exposure to pets is unclear, with conflicting data.¹³²⁻¹³⁴ Two recent studies have shown that cat but not dog ownership enhanced the effect of filaggrin mutations in promoting the development of AD.^{135,136} While patients with AD are often sensitized to house dust mites, there is not strong evidence to show that dust mite avoidance strategies prevent AD.^{137,138} The most recent systematic review regarding early life microbial exposures found evidence that exposures to endotoxin, farm animals, and dogs may protect against AD.¹³⁹ The consumption of unpasteurized milk and acquired helminth infections may also be protective, but are not recommended measures because of their potential associated health risks.

No definitive conclusions can be drawn regarding early antibiotic exposure and the risk of AD.^{85,140,141} Although studies are inconsistent, personal and second hand/household smoking status do not appear to significantly affect AD development¹⁴²⁻¹⁴⁵; however, smoking is detrimental to those with asthma and has many other negative health risks.

GAPS IN RESEARCH

In review of the currently available highest level of evidence, the expert work group acknowledges that while much is known about the diagnosis and evaluation of AD, much has yet to be learned. Significant gaps in research were identified, including but not limited to: validation studies of the AAD workgroup diagnostic criteria, development, validation, and uniformity in use of disease severity and quality of life measurements applicable to a busy clinical practice environment, interventional studies testing impact of multidisciplinary management on AD outcomes, and additional quality, controlled studies on epidemiologic risk factors for disease. It is hoped that additional

knowledge of AD pathogenesis will soon lead to a proven biomarker for diagnosis and/or monitoring, and that AD-associated pruritus is better understood to generate improved therapeutic options.

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The information below represents the authors' identified relationships with industry that are relevant to the guideline. Relevant relationships requiring recusal for drafting of guideline recommendations and content were not noted for this section.

Lawrence F. Eichenfield, MD: Dr Eichenfield served as a consultant for Anacor, Bayer, and Leo Pharma receiving honoraria and TopMD receiving stock options; was a consultant and speaker for Galderma, receiving honoraria; served as a consultant, speaker, and member of the advisory board for Medicis/Valeant, receiving honoraria; and was an investigator for Anacor, Astellas, Galderma, and Leo Pharma, receiving no compensation.

Sarah L. Chamlin, MD: Dr Chamlin served on the advisory boards for Galderma and Valeant, receiving honoraria.

Steven R. Feldman, MD, PhD: Dr Feldman served on the advisory boards for Amgen, Doak, Galderma, Pfizer, Pharmaderm, Skin Medica, and Stiefel, receiving honoraria; was a consultant for Abbott, Astellas, Caremark, Coria, Gerson Lehrman, Kikaku, Leo Pharma, Medicis, Merck, Merz, Novan, Peplin, and Pfizer receiving honoraria and Celgene, HanAll, and Novartis receiving other financial benefits; was a speaker for Abbott, Amgen, Astellas, Centocor, Dermatology Foundation, Galderma, Leo Pharma, Novartis, Pharmaderm, Sanofi-Aventis, Stiefel, and Taro, receiving honoraria; served as a stockholder and founder for Causa Technologies and

Medical Quality Enhancement Corporation, receiving stock; served as an investigator for Abbott, Amgen, Anacor, Astellas, Basilea, Celgene, Centocor, Galderma, Medicis, Skin Medica, and Steifel, receiving grants, and Suncare Research, receiving honoraria; and had other relationships with Informa, UptoDate, and Xlibris receiving royalty and Medscape receiving honoraria.

Jon M. Hanifin, MD: Dr Hanifin served on the advisory board for Chugai Pharma USA receiving honoraria; was a consultant for GlaxoSmithKline, Merck Elocon Advisory Board, Pfizer, and Valeant Elidel Advisory Board receiving honoraria; and served as an investigator for Asubio and Merck Sharp & Dohme receiving grants.

Eric L. Simpson, MD: Dr Simpson served as a consultant for Asubio, Brickell Biotech, Galderma, Medicis, Panmira Pharmaceuticals, and Regeneron, and a speaker for Centocor and Galderma receiving honoraria; and was an investigator for Amgen, Celgene, Galderma, and Regeneron receiving other financial benefits.

James N. Bergman, MD: Dr Bergman served as a speaker and consultant for Pediapharm receiving honoraria.

David E. Cohen, MD: Dr Cohen served on the advisory boards and as a consultant for Onset, Ferndale Labs, and Galderma, receiving honoraria; served on the board of directors and as a consultant for Brickell Biotechnology and Topica receiving honoraria, stock, and stock options; and was a consultant for Dermira and Dr Tatoff receiving honoraria and stock options.

Alfons Krol, MD: Dr Krol served as an investigator for Pierre-Fabre receiving grants.

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Robert A. Silverman, MD: Dr Silverman served as a speaker for Galderma and Promius receiving honoraria.

Craig A. Elmets, MD: Dr Elmets served on a data safety monitoring board for Astellas receiving honoraria.

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