

Guidelines of care for the management of atopic dermatitis

Section 1. Diagnosis and assessment of atopic dermatitis

Work Group: Co-chair, Lawrence F. Eichenfield, MD,^a Wynn L. Tom, MD,^a Sarah L. Chamlin, MD, MSCI,^b Steven R. Feldman, MD, PhD,^c Jon M. Hanifin, MD,^d Eric L. Simpson, MD,^d Timothy G. Berger, MD,^e James N. Bergman, MD,^f David E. Cohen, MD,^g Kevin D. Cooper, MD,^h Kelly M. Cordoro, MD,^e Dawn M. Davis, MD,ⁱ Alfons Krol, MD,^d David J. Margolis, MD, PhD,^j Amy S. Paller, MS, MD,^k Kathryn Schwarzenberger, MD,^l Robert A. Silverman, MD,^m Hywel C. Williams, PhD,ⁿ Craig A. Elmets, MD,^o Julie Block, BA,^p Christopher G. Harrod, MS,^q Wendy Smith Begolka, MBS,^q and Co-chair, Robert Sidbury, MD^f

San Diego, San Francisco, and San Rafael, California; Chicago and Schaumburg, Illinois; Winston-Salem, North Carolina; Portland, Oregon; Vancouver, British Columbia, Canada; New York, New York; Cleveland, Ohio; Rochester, Minnesota; Philadelphia, Pennsylvania; Burlington, Vermont; Fairfax, Virginia; Nottingham, United Kingdom; Birmingham, Alabama; and Seattle, Washington

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 2014;70:338-51.)

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

From the Division of Pediatric and Adolescent Dermatology,^a Rady Children's Hospital San Diego; Department of Dermatology,^b Ann and Robert H. Lurie Children's Hospital of Chicago; Department of Dermatology,^c Wake Forest University Health Sciences, Winston-Salem; Department of Dermatology,^d Oregon Health and Science University; Department of Dermatology,^e University of California San Francisco; Department of Dermatology and Skin Science,^f University of British Columbia; Ronald O. Perelman Department of Dermatology,^g New York University School of Medicine; Department of Dermatology,^h Case Western University, Cleveland; Department of Dermatology,ⁱ Mayo Clinic, Rochester; Department of Biostatistics and Epidemiology,^j University of Pennsylvania School of Medicine; Department of Dermatology,^k Northwestern University Feinberg School of Medicine; Division of Dermatology,^l Fletcher Allen Health Care, Burlington; private practice,^m Fairfax; Centre of Evidence-Based Dermatology,ⁿ Nottingham University

Hospitals NHS Trust, Nottingham; Department of Dermatology,^o University of Alabama at Birmingham; National Eczema Association,^p San Rafael; American Academy of Dermatology,^q Schaumburg; and the Department of Dermatology,^r Seattle Children's Hospital.

Funding sources: None.

The authors' conflicts of interest/disclosure statements appear at the end of the article.

Accepted for publication October 5, 2013.

Reprint requests: Wendy Smith Begolka, MBS, American Academy of Dermatology, 930 E Woodfield Rd, Schaumburg, IL 60173.

E-mail: wsmithbegolka@aad.org.

Published online December 2, 2013.

0190-9622/\$36.00

© 2013 by the American Academy of Dermatology, Inc.

<http://dx.doi.org/10.1016/j.jaad.2013.10.010>

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

-
- 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.

We thank Melinda Jen, MD, Michael Osofsky, MD, Kathleen Muldowney, MLS, Charmiel McDaniels, MS, and Tammi Matillano for technical assistance in the development of this manuscript. We also thank the AAD Board of Directors, the Council on Science and Research, the Clinical Guidelines Committee, and all commenting Academy members for their thoughtful and excellent comments.

Dr Tom is supported by a National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases research career development grant (K23AR060274). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Arthritis and Musculoskeletal and Skin Diseases or the National Institutes of Health.

The American Academy of Dermatology (AAD) strives to produce clinical guidelines that reflect the best available evidence supplemented with the judgment of expert clinicians. Significant efforts are taken to minimize the potential for conflicts of interest to influence guideline content. Funding of guideline production by medical or pharmaceutical entities is prohibited, full disclosure is obtained and evaluated for all guideline contributors, and recusal is used to manage identified relationships. The AAD conflict of interest policy summary may be viewed at www.aad.org.

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.

Amy S. Paller, MD: Dr Paller served as a consultant to AbbVie, Alwyn, Amgen, Galderma, GlaxoSmithKline, Leo Pharma, Lundbeck, Medicis, Pfizer, Promius, Sanofi/Regeneron, and TopMD receiving honoraria; and was an investigator for Amgen, Galderma, and Leo Pharma receiving no compensation.

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.

Robert Sidbury, MD, Wynnis L. Tom, MD, Timothy M. Berger, MD, Kevin D. Cooper, MD, Kelly M. Cordero, MD, Dawn M. Davis, MD, David J. Margolis, MD, PhD, Kathryn Schwarzenberger, MD, Hywel C. Williams, PhD, Julie Block, Christopher G. Harrod, MS, and Wendy Smith Begolka, MBS, have no relevant relationships to disclose.

REFERENCES

- Nankervis H, Maplethorpe A, Williams HC. Mapping randomized controlled trials of treatments for eczema—the GREAT database (the Global Resource of Eczema Trials: a collection of key data on randomized controlled trials of treatments for eczema from 2000 to 2010). *BMC Dermatol* 2011;11:10.
- Hanifin JM, Cooper KD, Ho VC, Kang S, Krafchik BR, Margolis DJ, et al. Guidelines of care for atopic dermatitis, developed in accordance with the American Academy of Dermatology (AAD)/American Academy of Dermatology Association "Administrative Regulations for Evidence-Based Clinical Practice Guidelines". *J Am Acad Dermatol* 2004;50:391-404.
- Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, Gelmetti C, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. *J Eur Acad Dermatol Venereol* 2012; 26:1176-93.
- Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, Gelmetti C, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. *J Eur Acad Dermatol Venereol* 2012; 26:1045-60.
- Schneider L, Tilles S, Lio P, Boguniewicz M, Beck L, LeBovidge J, et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol* 2013;131:295-9, e1-27.
- Ebell MH, Siwek J, Weiss BD, Woolf SH, Susman J, Ewigman B, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *J Am Board Fam Pract* 2004;17:59-67.
- American Academy of Dermatology web site. Administrative regulations. Evidence-based clinical practice guidelines. Available at: <http://www.aad.org/Forms/Policies/Uploads/AR/AR%20-%20Evidence-Based%20Clinical%20Guideline.pdf>. Accessed November 15, 2011.
- Kay J, Gawkrödger DJ, Mortimer MJ, Jaron AG. The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol* 1994;30:35-9.
- Perkin MR, Strachan DP, Williams HC, Kennedy CT, Golding J, Team AS. Natural history of atopic dermatitis and its relationship to serum total immunoglobulin E in a population-based birth cohort study. *Pediatr Allergy Immunol* 2004;15:221-9.
- Ellis CN, Mancini AJ, Paller AS, Simpson EL, Eichenfield LF. Understanding and managing atopic dermatitis in adult patients. *Semin Cutan Med Surg* 2012;31(3 Suppl):S18-22.
- Rudzki E, Samochocki Z, Rebandel P, Saciuk E, Galecki W, Raczka A, et al. Frequency and significance of the major and minor features of Hanifin and Rajka among patients with atopic dermatitis. *Dermatology* 1994;189:41-6.
- Mevorah B, Frenk E, Wietlisbach V, Carrel CF. Minor clinical features of atopic dermatitis. Evaluation of their diagnostic significance. *Dermatologica* 1988;177:360-4.
- Gu H, Chen XS, Chen K, Yan Y, Jing H, Chen XQ, et al. Evaluation of diagnostic criteria for atopic dermatitis: validity of the criteria of Williams et al. in a hospital-based setting. *Br J Dermatol* 2001;145:428-33.
- Haileamlak A, Lewis SA, Britton J, Venn AJ, Woldemariam D, Hubbard R, et al. Validation of the International Study of Asthma and Allergies in Children (ISAAC) and U.K. criteria for atopic eczema in Ethiopian children. *Br J Dermatol* 2005;152: 735-41.
- Lan CC, Lee CH, Lu YW, Lin CL, Chiu HH, Chou TC, et al. Prevalence of adult atopic dermatitis among nursing staff in a Taiwanese medical center: a pilot study on validation of diagnostic questionnaires. *J Am Acad Dermatol* 2009;61:806-12.
- Diepgen TL, Sauerbrei W, Fartasch M. Development and validation of diagnostic scores for atopic dermatitis incorporating criteria of data quality and practical usefulness. *J Clin Epidemiol* 1996;49:1031-8.
- De D, Kanwar AJ, Handa S. Comparative efficacy of Hanifin and Rajka's criteria and the UK working party's diagnostic criteria in diagnosis of atopic dermatitis in a hospital setting in North India. *J Eur Acad Dermatol Venereol* 2006; 20:853-9.
- Loden M, Andersson AC, Lindberg M. The number of diagnostic features in patients with atopic dermatitis correlates with dryness severity. *Acta Derm Venereol* 1998;78:387-8.
- Samochocki Z, Dejewski J. A comparison of criteria for diagnosis of atopic dermatitis in children. *World J Pediatr* 2012;8:355-8.

20. Samochocki Z, Paulochowska E, Zabielski S. Prognostic value of Hanifin and Rajka's feature sets in adult atopic dermatitis patients. *J Med* 2000;31:177-82.
21. Chalmers DA, Todd G, Saxe N, Milne JT, Tolosana S, Ngcelwane PN, et al. Validation of the U.K. Working Party diagnostic criteria for atopic eczema in a Xhosa-speaking African population. *Br J Dermatol* 2007;156:111-6.
22. Firooz A, Davoudi SM, Farahmand AN, Majdzadeh R, Kashani N, Dowlati Y. Validation of the diagnostic criteria for atopic dermatitis. *Arch Dermatol* 1999;135:514-6.
23. Saeki H, Iizuka H, Mori Y, Akasaka T, Takagi H, Kitajima Y, et al. Community validation of the U.K. diagnostic criteria for atopic dermatitis in Japanese elementary schoolchildren. *J Dermatol Sci* 2007;47:227-31.
24. Eichenfield LF, Hanifin JM, Luger TA, Stevens SR, Pride HB. Consensus conference on pediatric atopic dermatitis. *J Am Acad Dermatol* 2003;49:1088-95.
25. Johnke H, Vach W, Norberg LA, Bindslev-Jensen C, Host A, Andersen KE. A comparison between criteria for diagnosing atopic eczema in infants. *Br J Dermatol* 2005;153:352-8.
26. Williams HC. Clinical practice. Atopic dermatitis. *N Engl J Med* 2005;352:2314-24.
27. Brenninkmeijer EE, Schram ME, Leeftang MM, Bos JD, Spuls PI. Diagnostic criteria for atopic dermatitis: a systematic review. *Br J Dermatol* 2008;158:754-65.
28. Kabashima K. New concept of the pathogenesis of atopic dermatitis: interplay among the barrier, allergy, and pruritus as a trinity. *J Dermatol Sci* 2013;70:3-11.
29. Arbes SJ Jr, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 2005;116:377-83.
30. Murat-Susic S, Lipozencic J, Zizic V, Husar K, Marinovic B. Serum eosinophil cationic protein in children with atopic dermatitis. *Int J Dermatol* 2006;45:1156-60.
31. Schulte-Herbruggen O, Folster-Holst R, von Elstermann M, Augustin M, Hellweg R. Clinical relevance of nerve growth factor serum levels in patients with atopic dermatitis and psoriasis. *Int Arch Allergy Immunol* 2007;144:211-6.
32. Amon U, Memmel U, Stoll R, Amon S. Comparison of severity scoring of atopic dermatitis values and serum levels of eosinophil cationic protein and mast cell tryptase for routine evaluation of atopic dermatitis. *Acta Derm Venereol* 2000;80:284-6.
33. Dhar S, Malakar R, Chattopadhyay S, Banerjee R, Ghosh A. Correlation of the severity of atopic dermatitis with absolute eosinophil counts in peripheral blood and serum IgE levels. *Indian J Dermatol Venereol Leprol* 2005;71:246-9.
34. Gerdes S, Kurrat W, Mrowietz U. Serum mast cell tryptase is not a useful marker for disease severity in psoriasis or atopic dermatitis. *Br J Dermatol* 2009;160:736-40.
35. Aral M, Arican O, Gul M, Sasmaz S, Kocturk SA, Kastal U, et al. The relationship between serum levels of total IgE, IL-18, IL-12, IFN-gamma and disease severity in children with atopic dermatitis. *Mediators Inflamm* 2006;2006:73098.
36. Di Lorenzo G, Gangemi S, Merendino RA, Minciullo PL, Cannavo SP, Martinelli N, et al. Serum levels of soluble CD30 in adult patients affected by atopic dermatitis and its relation to age, duration of disease and Scoring Atopic Dermatitis index. *Mediators Inflamm* 2003;12:123-5.
37. El Mongy S, Metwaly SS, Arafat MS, Hady HA. Serum levels of soluble CD30 in patients with atopic dermatitis: correlations with age, disease duration and severity. *Egypt J Immunol* 2008;15:123-9.
38. Ezzat MH, Hasan ZE, Shaheen KY. Serum measurement of interleukin-31 (IL-31) in paediatric atopic dermatitis: elevated levels correlate with severity scoring. *J Eur Acad Dermatol Venereol* 2011;25:334-9.
39. Jahnz-Rozyk K, Targowski T, Paluchowska E, Owczarek W, Kucharczyk A. Serum thymus and activation-regulated chemokine, macrophage-derived chemokine and eotaxin as markers of severity of atopic dermatitis. *Allergy* 2005;60:685-8.
40. Nakazato J, Kishida M, Kuroiwa R, Fujiwara J, Shimoda M, Shinomiya N. Serum levels of Th2 chemokines, CCL17, CCL22, and CCL27, were the important markers of severity in infantile atopic dermatitis. *Pediatr Allergy Immunol* 2008;19:605-13.
41. Rodriguez E, Baurecht H, Herberich E, Wagenpfeil S, Brown SJ, Cordell HJ, et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease. *J Allergy Clin Immunol* 2009;123:1361-70.e7.
42. Peters AS, Kellberger J, Vogelberg C, Dressel H, Windstetter D, Weinmayr G, et al. Prediction of the incidence, recurrence, and persistence of atopic dermatitis in adolescence: a prospective cohort study. *J Allergy Clin Immunol* 2010;126:590-5, e1-3.
43. Rehal B, Armstrong AW. Health outcome measures in atopic dermatitis: a systematic review of trends in disease severity and quality-of-life instruments 1985-2010. *PloS one* 2011;6:e17520.
44. Schmitt J, Langan S, Williams HC. What are the best outcome measurements for atopic eczema? A systematic review. *J Allergy Clin Immunol* 2007;120:1389-98.
45. Schram ME, Spuls PI, Leeftang MM, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. *Allergy* 2012;67:99-106.
46. Charman DP, Varigos GA. Grades of severity and the validation of an atopic dermatitis assessment measure (ADAM). *J Outcome Meas* 1999;3:162-75.
47. Carel K, Bratton DL, Miyazawa N, Gyorkos E, Kelsay K, Bender B, et al. The Atopic Dermatitis Quickscore (ADQ): validation of a new parent-administered atopic dermatitis scoring tool. *Ann Allergy Asthma Immunol* 2008;101:500-7.
48. Sprickelman AB, Tupker RA, Burgerhof H, Schouten JP, Brand PL, Heymans HS, et al. Severity scoring of atopic dermatitis: a comparison of three scoring systems. *Allergy* 1997;52:944-9.
49. Angelova-Fischer I, Bauer A, Hipler UC, Petrov I, Kazandjieva J, Bruckner T, et al. The objective severity assessment of atopic dermatitis (OSAAD) score: validity, reliability and sensitivity in adult patients with atopic dermatitis. *Br J Dermatol* 2005;153:767-73.
50. Charman CR, Venn AJ, Williams H. Measuring atopic eczema severity visually: which variables are most important to patients? *Arch Dermatol* 2005;141:1146-51.
51. Stalder JF, Barbarot S, Wollenberg A, Holm EA, De Raeve L, Seidenari S, et al. Patient-Oriented SCORAD (PO-SCORAD): a new self-assessment scale in atopic dermatitis validated in Europe. *Allergy* 2011;66:1114-21.
52. Housman TS, Patel MJ, Camacho F, Feldman SR, Fleischer AB Jr, Balkrishnan R. Use of the Self-Administered Eczema Area and Severity Index by parent caregivers: results of a validation study. *Br J Dermatol* 2002;147:1192-8.
53. van Velsen SG, Knol MJ, Haeck IM, Bruijnzeel-Koomen CA, Pasmans SG. The Self-administered Eczema Area and Severity Index in children with moderate to severe atopic dermatitis:

- better estimation of AD body surface area than severity. *Pediatr Dermatol* 2010;27:470-5.
54. Wolkerstorfer A, de Waard van der Spek FB, Glazenburg EJ, Mulder PG, Oranje AP. Scoring the severity of atopic dermatitis: three item severity score as a rough system for daily practice and as a pre-screening tool for studies. *Acta Derm Venereol* 1999;79:356-9.
 55. Jemec GB, Esmann S, Holm EA, Tycho A, Jorgensen TM. Time spent on treatment (TSOT). An independent assessment of disease severity in atopic dermatitis. *Acta Dermatovenerol Alp Panonica Adriat* 2006;15:119-24.
 56. Holm EA, Jemec GB. Time spent on treatment of atopic dermatitis: a new method of measuring pediatric morbidity? *Pediatr Dermatol* 2004;21:623-7.
 57. Schmitt J, Spuls P, Boers M, Thomas K, Chalmers J, Roekevisch E, et al. Towards global consensus on outcome measures for atopic eczema research: results of the HOME II meeting. *Allergy* 2012;67:1111-7.
 58. Chamlin SL, Lai JS, Cella D, Frieden IJ, Williams ML, Mancini AJ, et al. Childhood Atopic Dermatitis Impact Scale: reliability, discriminative and concurrent validity, and responsiveness. *Arch Dermatol* 2007;143:768-72.
 59. Lewis-Jones MS, Finlay AY, Dykes PJ. The Infants' Dermatitis Quality of Life Index. *Br J Dermatol* 2001;144:104-10.
 60. Augustin M, Lange S, Wenninger K, Seidenglanz K, Amon U, Zschocke I. Validation of a comprehensive Freiburg Life Quality Assessment (FLQA) core questionnaire and development of a threshold system. *Eur J Dermatol* 2004;14:107-13.
 61. Evers AW, Duller P, van de Kerkhof PC, van der Valk PG, de Jong EM, Gerritsen MJ, et al. The Impact of Chronic Skin Disease on Daily Life (ISDL): a generic and dermatology-specific health instrument. *Br J Dermatol* 2008;158:101-8.
 62. Smidt AC, Lai JS, Cella D, Patel S, Mancini AJ, Chamlin SL. Development and validation of Skindex-Teen, a quality-of-life instrument for adolescents with skin disease. *Arch Dermatol* 2010;146:865-9.
 63. Kondo-Endo K, Ohashi Y, Nakagawa H, Katsunuma T, Ohya Y, Kamibeppu K, et al. Development and validation of a questionnaire measuring quality of life in primary caregivers of children with atopic dermatitis (QPCAD). *Br J Dermatol* 2009;161:617-25.
 64. Chren MM, Lasek RJ, Sahay AP, Sands LP. Measurement properties of Skindex-16: a brief quality-of-life measure for patients with skin diseases. *J Cutan Med Surg* 2001;5:105-10.
 65. Wittkowski A, Richards HL, Griffiths CE, Main CJ. The impact of psychological and clinical factors on quality of life in individuals with atopic dermatitis. *J Psychosom Res* 2004;57:195-200.
 66. Linnet J, Jemec GB. An assessment of anxiety and dermatology life quality in patients with atopic dermatitis. *Br J Dermatol* 1999;140:268-72.
 67. Hon KL, Kam WY, Lam MC, Leung TF, Ng PC. CDLQI, SCORAD and NESS: are they correlated? *Qual Life Res* 2006;15:1551-8.
 68. Misery L, Finlay AY, Martin N, Boussetta S, Nguyen C, Myon E, et al. Atopic dermatitis: impact on the quality of life of patients and their partners. *Dermatology* 2007;215:123-9.
 69. Chamlin SL, Mattson CL, Frieden IJ, Williams ML, Mancini AJ, Cella D, et al. The price of pruritus: sleep disturbance and cosleeping in atopic dermatitis. *Arch Pediatr Adolesc Med* 2005;159:745-50.
 70. Hon KL, Leung TF, Wong KY, Chow CM, Chuh A, Ng PC. Does age or gender influence quality of life in children with atopic dermatitis? *Clin Exp Dermatol* 2008;33:705-9.
 71. Dawn A, Papoiu AD, Chan YH, Rapp SR, Rassette N, Yosipovitch G. Itch characteristics in atopic dermatitis: results of a web-based questionnaire. *Br J Dermatol* 2009;160:642-4.
 72. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *Int J Clin Pract* 2006;60:984-92.
 73. Weisshaar E, Diepgen TL, Bruckner T, Fartasch M, Kupfer J, Lob-Corzilius T, et al. Itch intensity evaluated in the German Atopic Dermatitis Intervention Study (GADIS): correlations with quality of life, coping behaviour and SCORAD severity in 823 children. *Acta Derm Venereol* 2008;88:234-9.
 74. Ricci G, Bendandi B, Bellini F, Patrizi A, Masi M. Atopic dermatitis: quality of life of young Italian children and their families and correlation with severity score. *Pediatr Allergy Immunol* 2007;18:245-9.
 75. Bender BG, Ballard R, Canono B, Murphy JR, Leung DY. Disease severity, scratching, and sleep quality in patients with atopic dermatitis. *J Am Acad Dermatol* 2008;58:415-20.
 76. Ben-Gashir MA, Seed PT, Hay RJ. Are quality of family life and disease severity related in childhood atopic dermatitis? *J Eur Acad Dermatol Venereol* 2002;16:455-62.
 77. Batlles-Garrido J, Torres-Borrego J, Rubi-Ruiz T, Bonillo-Perales A, Gonzalez-Jimenez Y, Momblan-De Cabo J, et al. Prevalence and factors linked to allergic rhinitis in 10 and 11-year-old children in Almeria. Isaac Phase II, Spain. *Allergol Immunopathol (Madr)* 2010;38:135-41.
 78. Chawes BL, Bonnelykke K, Kreiner-Moller E, Bisgaard H. Children with allergic and nonallergic rhinitis have a similar risk of asthma. *J Allergy Clin Immunol* 2010;126:567-73.
 79. Sultesz M, Katona G, Hirschberg A, Galffy G. Prevalence and risk factors for allergic rhinitis in primary schoolchildren in Budapest. *Int J Pediatr Otorhinolaryngol* 2010;74:503-9.
 80. Kyllonen H, Malmberg P, Remitz A, Ryttila P, Metso T, Helenius I, et al. Respiratory symptoms, bronchial hyper-responsiveness, and eosinophilic airway inflammation in patients with moderate-to-severe atopic dermatitis. *Clin Exp Allergy* 2006;36:192-7.
 81. Hwang CY, Chen YJ, Lin MW, Chen TJ, Chu SY, Chen CC, et al. Prevalence of atopic dermatitis, allergic rhinitis and asthma in Taiwan: a national study 2000 to 2007. *Acta Derm Venereol* 2010;90:589-94.
 82. Hyvarinen MK, Kotaniemi-Syrjanen A, Reijonen TM, Korhonen K, Korppi MO. Teenage asthma after severe early childhood wheezing: an 11-year prospective follow-up. *Pediatr Pulmonol* 2005;40:316-23.
 83. Eller E, Kjaer HF, Host A, Andersen KE, Bindslev-Jensen C. Food allergy and food sensitization in early childhood: results from the DARC cohort. *Allergy* 2009;64:1023-9.
 84. Horwitz AA, Hossain J, Yousef E. Correlates of outcome for atopic dermatitis. *Ann Allergy Asthma Immunol* 2009;103:146-51.
 85. Flohr C, Pascoe D, Williams HC. Atopic dermatitis and the 'hygiene hypothesis': too clean to be true? *Br J Dermatol* 2005;152:202-16.
 86. Spergel JM. From atopic dermatitis to asthma: the atopic march. *Ann Allergy Asthma Immunol* 2010;105:99-106.
 87. van der Hulst AE, Klip H, Brand PL. Risk of developing asthma in young children with atopic eczema: a systematic review. *J Allergy Clin Immunol* 2007;120:565-9.
 88. Flohr C, Weiland SK, Weinmayr G, Bjorksten B, Braback L, Brunekreef B, et al. The role of atopic sensitization in flexural eczema: findings from the International Study of Asthma and Allergies in Childhood Phase Two. *J Allergy Clin Immunol* 2008;121:141-7.e4.
 89. Camfferman D, Kennedy JD, Gold M, Martin AJ, Winwood P, Lushington K. Eczema, sleep, and behavior in children. *J Clin Sleep Med* 2010;6:581-8.

90. Hanifin JM, Reed ML, Eczema Prevalence and Impact Working Group. A population-based survey of eczema prevalence in the United States. *Dermatitis* 2007;18:82-91.
91. Camfferman D, Kennedy JD, Gold M, Martin AJ, Lushington K. Eczema and sleep and its relationship to daytime functioning in children. *Sleep Med Rev* 2010;14:359-69.
92. Bashir K, Dar NR, Rao SU. Depression in adult dermatology outpatients. *J Coll Physicians Surg Pak* 2010;20:811-3.
93. Schmitt J, Romanos M, Pfennig A, Leopold K, Meurer M. Psychiatric comorbidity in adult eczema. *Br J Dermatol* 2009;161:878-83.
94. Schmitt J, Romanos M, Schmitt NM, Meurer M, Kirch W. Atopic eczema and attention-deficit/hyperactivity disorder in a population-based sample of children and adolescents. *JAMA* 2009;301:724-6.
95. Yaghmaie P, Koudelka CW, Simpson EL. Mental health comorbidity in patients with atopic dermatitis. *J Allergy Clin Immunol* 2013;131:428-33.
96. Harding NJ, Birch JM, Hepworth SJ, McKinney PA. Atopic dysfunction and risk of central nervous system tumours in children. *Eur J Cancer* 2008;44:92-9.
97. Synnerstad I, Fredrikson M, Ternesten-Bratel A, Rosdahl I. Low risk of melanoma in patients with atopic dermatitis. *J Eur Acad Dermatol Venereol* 2008;22:1423-8.
98. Vajdic CM, Falster MO, de Sanjose S, Martinez-Maza O, Becker N, Bracci PM, et al. Atopic disease and risk of non-Hodgkin lymphoma: an InterLymph pooled analysis. *Cancer Res* 2009;69:6482-9.
99. Tennis P, Gelfand JM, Rothman KJ. Evaluation of cancer risk related to atopic dermatitis and use of topical calcineurin inhibitors. *Br J Dermatol* 2011;165:465-73.
100. Wang H, Diepgen TL. Atopic dermatitis and cancer risk. *Br J Dermatol* 2006;154:205-10.
101. Silverberg JI, Kleiman E, Lev-Tov H, Silverberg NB, Durkin HG, Joks R, et al. Association between obesity and atopic dermatitis in childhood: a case-control study. *J Allergy Clin Immunol* 2011;127:1180-6.e1.
102. Murray CS, Canoy D, Buchan I, Woodcock A, Simpson A, Custovic A. Body mass index in young children and allergic disease: gender differences in a longitudinal study. *Clin Exp Allergy* 2011;41:78-85.
103. Kajbaf TZ, Asar S, Alipoor MR. Relationship between obesity and asthma symptoms among children in Ahvaz, Iran: a cross sectional study. *Ital J Pediatr* 2011;37:1.
104. Vlaski E, Stavric K, Isjanovska R, Seckova L, Kimovska M. Overweight hypothesis in asthma and eczema in young adolescents. *Allergol Immunopathol (Madr)* 2006;34:199-205.
105. Agostoni C, Grandi F, Scaglioni S, Gianni ML, Torcoletti M, Radaelli G, et al. Growth pattern of breastfed and nonbreastfed infants with atopic dermatitis in the first year of life. *Pediatrics* 2000;106:E73.
106. Palit A, Handa S, Bhalla AK, Kumar B. A mixed longitudinal study of physical growth in children with atopic dermatitis. *Indian J Dermatol Venereol Leprol* 2007;73:171-5.
107. Boguniewicz M, Nicol N, Kelsay K, Leung DY. A multidisciplinary approach to evaluation and treatment of atopic dermatitis. *Semin Cutan Med Surg* 2008;27:115-27.
108. Ricci G, Bendandi B, Aiazzi R, Patrizi A, Masi M. Three years of Italian experience of an educational program for parents of young children affected by atopic dermatitis: improving knowledge produces lower anxiety levels in parents of children with atopic dermatitis. *Pediatr Dermatol* 2009;26:1-5.
109. Wen HJ, Chen PC, Chiang TL, Lin SJ, Chuang YL, Guo YL. Predicting risk for early infantile atopic dermatitis by hereditary and environmental factors. *Br J Dermatol* 2009;161:1166-72.
110. Wadonda-Kabondo N, Sterne JA, Golding J, Kennedy CT, Archer CB, Dunnill MG, et al. Association of parental eczema, hayfever, and asthma with atopic dermatitis in infancy: birth cohort study. *Arch Dis Childhood* 2004;89:917-21.
111. Kuster W, Petersen M, Christophers E, Goos M, Sterry W. A family study of atopic dermatitis. Clinical and genetic characteristics of 188 patients and 2, 151 family members. *Arch Dermatol Res* 1990;282:98-102.
112. Ruiz RG, Kemeny DM, Price JF. Higher risk of infantile atopic dermatitis from maternal atopy than from paternal atopy. *Clin Exp Allergy* 1992;22:762-6.
113. Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. *N Engl J Med* 2011;365:1315-27.
114. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006;38:441-6.
115. Bager P, Wohlfahrt J, Westergaard T. Caesarean delivery and risk of atopy and allergic disease: meta-analyses. *Clin Exp Allergy* 2008;38:634-42.
116. Civelek E, Sahiner UM, Yuksel H, Boz AB, Orhan F, Uner A, et al. Prevalence, burden, and risk factors of atopic eczema in schoolchildren aged 10-11 years: a national multicenter study. *J Investig Allergol Clin Immunol* 2011;21:270-7.
117. Lundholm C, Ortqvist AK, Lichtenstein P, Cnattingius S, Almqvist C. Impaired fetal growth decreases the risk of childhood atopic eczema: a Swedish twin study. *Clin Exp Allergy* 2010;40:1044-53.
118. Moore MM, Rifas-Shiman SL, Rich-Edwards JW, Kleinman KP, Camargo CA Jr, Gold DR, et al. Perinatal predictors of atopic dermatitis occurring in the first six months of life. *Pediatrics* 2004;113:468-74.
119. Greer FR, Sicherer SH, Burks AW, American Academy of Pediatrics Committee on Nutrition, American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008;121:183-91.
120. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database Syst Rev* 2012;9:CD000133.
121. Yang YW, Tsai CL, Lu CY. Exclusive breastfeeding and incident atopic dermatitis in childhood: a systematic review and meta-analysis of prospective cohort studies. *Br J Dermatol* 2009;161:373-83.
122. Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006:CD003664.
123. Alexander DD, Cabana MD. Partially hydrolyzed 100% whey protein infant formula and reduced risk of atopic dermatitis: a meta-analysis. *J Pediatr Gastroenterol Nutr* 2010;50:422-30.
124. Pelucchi C, Chatenoud L, Turati F, Galeone C, Moja L, Bach JF, et al. Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis. *Epidemiology* 2012;23:402-14.
125. Kuitunen M, Kukkonen K, Juntunen-Backman K, Korpela R, Poussa T, Tuure T, et al. Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort. *J Allergy Clin Immunol* 2009;123:335-41.

126. Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol* 2011;131:67-73.
127. Weber AS, Haidinger G. The prevalence of atopic dermatitis in children is influenced by their parents' education: results of two cross-sectional studies conducted in Upper Austria. *Pediatr Allergy Immunol* 2010;21:1028-35.
128. Martorell Aragones A, Felix Toledo R, Martorell Calatayud A, Cerda Mir JC. Epidemiologic, clinical and socioeconomic factors of atopic dermatitis in Spain: *Alergologica-2005*. *J Investig Allergol Clin Immunol* 2009;19(Suppl 2):27-33.
129. Purvis DJ, Thompson JM, Clark PM, Robinson E, Black PN, Wild CJ, et al. Risk factors for atopic dermatitis in New Zealand children at 3.5 years of age. *Br J Dermatol* 2005;152:742-9.
130. Schram ME, Tedja AM, Spijker R, Bos JD, Williams HC, Spuls PI. Is there a rural/urban gradient in the prevalence of eczema? A systematic review. *Br J Dermatol* 2010;162:964-73.
131. Cramer C, Link E, Bauer CP, Hoffmann U, von Berg A, Lehmann I, et al. Association between attendance of day care centres and increased prevalence of eczema in the German birth cohort study LISAplus. *Allergy* 2011;66:68-75.
132. Biagini Myers JM, Wang N, LeMasters GK, Bernstein DI, Epstein TG, Lindsey MA, et al. Genetic and environmental risk factors for childhood eczema development and allergic sensitization in the CCAAPS cohort. *J Invest Dermatol* 2010;130:430-7.
133. Langan SM, Flohr C, Williams HC. The role of furry pets in eczema: a systematic review. *Arch Dermatol* 2007;143:1570-7.
134. Epstein TG, Bernstein DI, Levin L, Khurana Hershey GK, Ryan PH, Reponen T, et al. Opposing effects of cat and dog ownership and allergic sensitization on eczema in an atopic birth cohort. *J Pediatr* 2011;158:265-71, e1-5.
135. Schuttelaar ML, Kerkhof M, Jonkman MF, Koppelman GH, Brunekreef B, de Jongste JC, et al. Filaggrin mutations in the onset of eczema, sensitization, asthma, hay fever and the interaction with cat exposure. *Allergy* 2009;64:1758-65.
136. Bisgaard H, Simpson A, Palmer CN, Bonnelykke K, McLean I, Mukhopadhyay S, et al. Gene-environment interaction in the onset of eczema in infancy: filaggrin loss-of-function mutations enhanced by neonatal cat exposure. *PLoS Med* 2008;5:e131.
137. Harris JM, Williams HC, White C, Moffat S, Mills P, Newman Taylor AJ, et al. Early allergen exposure and atopic eczema. *Br J Dermatol* 2007;156:698-704.
138. Teplitsky V, Mumcuoglu KY, Babai I, Dalal I, Cohen R, Tanay A. House dust mites on skin, clothes, and bedding of atopic dermatitis patients. *Int J Dermatol* 2008;47:790-5.
139. Flohr C, Yeo L. Atopic dermatitis and the hygiene hypothesis revisited. *Curr Probl Dermatol* 2011;41:1-34.
140. Schmitt J, Schmitt NM, Kirch W, Meurer M. Early exposure to antibiotics and infections and the incidence of atopic eczema: a population-based cohort study. *Pediatr Allergy Immunol* 2010;21:292-300.
141. Kusel MM, de Klerk N, Holt PG, Sly PD. Antibiotic use in the first year of life and risk of atopic disease in early childhood. *Clin Exp Allergy* 2008;38:1921-8.
142. Vlaski E, Stavic K, Seckova L, Kimovska M, Isjanovska R. Do household tobacco smoking habits influence asthma, rhinitis and eczema among 13-14 year-old adolescents? *Allergol Immunopathol (Madr)* 2011;39:39-44.
143. Bohme M, Kull I, Bergstrom A, Wickman M, Nordvall L, Pershagen G, et al. Parental smoking increases the risk for eczema with sensitization in 4-year-old children. *J Allergy Clin Immunol* 2010;125:941-3.
144. Bo K, Thoresen M, Dalgard F. Smokers report more psoriasis, but not atopic dermatitis or hand eczema: results from a Norwegian population survey among adults. *Dermatology* 2008;216:40-5.
145. Lee CH, Chuang HY, Hong CH, Huang SK, Chang YC, Ko YC, et al. Lifetime exposure to cigarette smoking and the development of adult-onset atopic dermatitis. *Br J Dermatol* 2011;164:483-9.
146. Firooz A, Kashani MN. Diagnostic criteria for atopic dermatitis. *J Eur Acad Dermatol Venereol* 2008;22:130.
147. Hamada M, Furusyo N, Urabe K, Morita K, Nakahara T, Kinukawa N, et al. Prevalence of atopic dermatitis and serum IgE values in nursery school children in Ishigaki Island, Okinawa, Japan. *J Dermatol* 2005;32:248-55.
148. Williams HC, Burney PG, Pembroke AC, Hay RJ. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. *Br J Dermatol* 1994;131:406-16.
149. Williams HC, Burney PG, Pembroke AC, Hay RJ. Validation of the U.K. diagnostic criteria for atopic dermatitis in a population setting. U.K. Diagnostic Criteria for Atopic Dermatitis Working Party. *Br J Dermatol* 1996;135:12-7.
150. Belloni Fortina A, Tonin E, Pigozzi B, Romano I, Michelotto G, Alaibac M. IL-16 serum level in children with atopic dermatitis. *Int J Immunopathol Pharmacol* 2006;19:841-5.
151. Gutgesell C, Heise S, Seubert A, Stichtenoth DO, Frolich JC, Neumann C. Comparison of different activity parameters in atopic dermatitis: correlation with clinical scores. *Br J Dermatol* 2002;147:914-9.
152. Hirai S, Kageshita T, Kimura T, Tsujisaki M, Okajima K, Imai K, et al. Soluble intercellular adhesion molecule-1 and soluble E-selectin levels in patients with atopic dermatitis. *Br J Dermatol* 1996;134:657-61.
153. Hon KL, Lam MC, Wong KY, Leung TF, Ng PC. Pathophysiology of nocturnal scratching in childhood atopic dermatitis: the role of brain-derived neurotrophic factor and substance P. *Br J Dermatol* 2007;157:922-5.
154. Horikawa T, Nakayama T, Hikita I, Yamada H, Fujisawa R, Bito T, et al. IFN-gamma-inducible expression of thymus and activation-regulated chemokine/CCL17 and macrophage-derived chemokine/CCL22 in epidermal keratinocytes and their roles in atopic dermatitis. *Int Immunol* 2002;14:767-73.
155. Kakinuma T, Saeki H, Tsunemi Y, Fujita H, Asano N, Mitsui H, et al. Increased serum cutaneous T cell-attracting chemokine (CCL27) levels in patients with atopic dermatitis and psoriasis vulgaris. *J Allergy Clin Immunol* 2003;111:592-7.
156. La Grutta S, Richiusa P, Pizzolanti G, Mattina A, Pajno GB, Citarrella R, et al. CD4(+)IL-13(+) cells in peripheral blood well correlates with the severity of atopic dermatitis in children. *Allergy* 2005;60:391-5.
157. Leung TF, Ma KC, Hon KL, Lam CW, Wan H, Li CY, et al. Serum concentration of macrophage-derived chemokine may be a useful inflammatory marker for assessing severity of atopic dermatitis in infants and young children. *Pediatr Allergy Immunol* 2003;14:296-301.
158. Mostafa GA, Tomoum HY, Salem SA, Abd El-Aziz MM, Abou El-Maged DI, El-Sayed El-Far I. Serum concentrations of CCR4 ligands in relation to clinical severity of atopic dermatitis in Egyptian children. *Pediatr Allergy Immunol* 2008;19:756-62.
159. Oflazoglu E, Simpson EL, Takiguchi R, Grewal IS, Hanifin JM, Gerber HP. CD30 expression on CD1a+ and CD8+ cells in atopic dermatitis and correlation with disease severity. *Eur J Dermatol* 2008;18:41-9.
160. Oflazoglu E, Simpson EL, Takiguchi R, Hanifin JM, Grewal IS, Gerber HP. CD40 expression on antigen presenting cells

- and correlation with disease severity in atopic dermatitis. *Eur J Dermatol* 2008;18:527-33.
161. Ott H, Wilke J, Baron JM, Hoger PH, Folster-Holst R. Soluble immune receptor serum levels are associated with age, but not with clinical phenotype or disease severity in childhood atopic dermatitis. *J Eur Acad Dermatol Venereol* 2010;24:395-402.
 162. Raap U, Werfel T, Goltz C, Deneka N, Langer K, Bruder M, et al. Circulating levels of brain-derived neurotrophic factor correlate with disease severity in the intrinsic type of atopic dermatitis. *Allergy* 2006;61:1416-8.
 163. Song TW, Sohn MH, Kim ES, Kim KW, Kim KE. Increased serum thymus and activation-regulated chemokine and cutaneous T cell-attracting chemokine levels in children with atopic dermatitis. *Clin Exp Allergy* 2006;36:346-51.
 164. Wolkerstorfer A, Laan MP, Savelkoul HF, Neijens HJ, Mulder PG, Oudesluys-Murphy AM, et al. Soluble E-selectin, other markers of inflammation and disease severity in children with atopic dermatitis. *Br J Dermatol* 1998;138:431-5.
 165. Vakirlis E, Lazaridou E, Tzellos TG, Gerou S, Chatzidimitriou D, Ioannides D. Investigation of cytokine levels and their association with SCORAD index in adults with acute atopic dermatitis. *J Eur Acad Dermatol Venereol* 2011;25:409-16.
 166. Wu KG, Li TH, Chen CJ, Cheng HI, Wang TY. Correlations of serum Interleukin-16, total IgE, eosinophil cationic protein and total eosinophil counts with disease activity in children with atopic dermatitis. *Int J Immunopathol Pharmacol* 2011;24:15-23.
 167. Barbier N, Paul C, Luger T, Allen R, De Prost Y, Papp K, et al. Validation of the Eczema Area and Severity Index for atopic dermatitis in a cohort of 1550 patients from the pimecrolimus cream 1% randomized controlled clinical trials programme. *Br J Dermatol* 2004;150:96-102.
 168. Charman CR, Venn AJ, Williams HC. Reliability testing of the Six Area, Six Sign Atopic Dermatitis severity score. *Br J Dermatol* 2002;146:1057-60.
 169. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Arch Dermatol* 2004;140:1513-9.
 170. Charman D, Varigos G, Horne DJ, Oberklaid F. The development of a practical and reliable assessment measure for atopic dermatitis (ADAM). *J Outcome Meas* 1999;3:21-34.
 171. Cosickic A, Skokic F, Colic-Hadzic B, Jahic M. Clinical characteristics and estimation severity of the atopic dermatitis in children. *Med Arh* 2010;64:178-82.
 172. Emerson RM, Charman CR, Williams HC. The Nottingham Eczema Severity Score: preliminary refinement of the Rajka and Langeland grading. *Br J Dermatol* 2000;142:288-97.
 173. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol* 2001;10:11-8.
 174. Holm EA, Wulf HC, Thomassen L, Jemec GB. Assessment of atopic eczema: clinical scoring and noninvasive measurements. *Br J Dermatol* 2007;157:674-80.
 175. Oranje AP, Stalder JF, Taieb A, Tasset C, de Longueville M. Scoring of atopic dermatitis by SCORAD using a training atlas by investigators from different disciplines. ETAC Study Group. *Early Treatment of the Atopic Child. Pediatr Allergy Immunol* 1997;8:28-34.
 176. Rullo VE, Segato A, Kirsh A, Sole D. Severity scoring of atopic dermatitis: a comparison of two scoring systems. *Allergol Immunopathol (Madr)* 2008;36:205-11.