Published in final edited form as:

J Am Acad Dermatol. 2014 December ; 71(6): 1218–1233. doi:10.1016/j.jaad.2014.08.038.

Guidelines of Care for the Management of Atopic Dermatitis Part 4: Prevention of Disease Flares and Use of Adjunctive Therapies and Approaches

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

^aDepartment of Dermatology, Seattle Children's Hospital, Seattle, WA

^bUniversity of California, San Diego and Division of Pediatric and Adolescent Dermatology, Rady Children's Hospital, San Diego, CA

^cDepartment of Dermatology and Skin Science, University of British Columbia, Vancouver, B.C

^dDepartment of Dermatology, Case Western University, Cleveland, OH

^ePrivate Practice, Fairfax, VA

^fDepartment of Dermatology, University of California San Francisco, San Francisco, CA

^gDepartment of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL

^hDepartment of Dermatology, New York University School of Medicine, New York, NY

ⁱDepartment of Dermatology, University of California San Francisco, San Francisco, CA

^jDepartment of Dermatology, Mayo Clinic, Rochester, MN

^kDepartment of Dermatology, Wake Forest University Health Sciences, Winston-Salem, NC

^lDepartment of Dermatology, Oregon Health & Science University, Portland, OR

^mDepartment of Dermatology, Oregon Health & Science University, Portland, OR

ⁿDepartment of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA

^oDepartment of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL

© 2014 Published by the American Academy of Dermatology, Inc.

*Corresponding Author and Reprint Requests: Wendy Smith Begolka, MBS, American Academy of Dermatology, 930 East Woodfield Road, Schaumburg, IL 60173, Ph: (847) 240-1762, FAX: (847) 330-1120, wsmithbegolka@aad.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

^PKaplan-Amonette Department of Dermatology, University of Tennessee Health Science Center, Memphis, TN

^QDepartment of Dermatology, Oregon Health & Science University, Portland, OR

^RCentre of Evidence-Based Dermatology, Nottingham University Hospitals NHS Trust, Nottingham, U.K

^SDepartment of Dermatology, University of Alabama at Birmingham, Birmingham, AL

^TNational Eczema Association, San Rafael, CA

^UAmerican Academy of Dermatology, Schaumburg, IL

^VAmerican Academy of Dermatology, Schaumburg, IL

^WUniversity of California, San Diego and Division of Pediatric and Adolescent Dermatology, Rady Children's Hospital, San Diego, CA

Abstract

Atopic dermatitis (AD) is a common, chronic inflammatory dermatosis that can affect all age groups. This evidence-based guideline addresses important clinical questions that arise in its management. In this final section, treatments for flare prevention and adjunctive and complementary therapies and approaches are reviewed. Suggestions on utilization are given based on available evidence.

Keywords

atopic dermatitis; flare; topicals; corticosteroids; calcineurin inhibitors; education; allergy testing; food allergy; aeroallergens; diet; complementary therapy

Scope

This guideline addresses the treatment of pediatric and adult atopic dermatitis (AD, atopic eczema) of all severities. The treatment of other forms of eczematous dermatitis is outside the scope of this document. Recommendations on AD management are subdivided into four sections given the significant breadth of the topic, and to update as well as expand on the clinical information and recommendations previously published in 2004. This document is the final in the series of four publications and discusses management and control of atopic dermatitis flares using topical modalities, and the utility and timing of allergen testing and avoidance. Also discussed is the use of adjunctive therapies and approaches such as environmental, dietary, and educational interventions, and complementary therapies.

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 management of flare progression and in the use of adjunctive therapies and approaches (Table I). Work group members completed a disclosure of interests which 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 search of the PubMed and the Global Resources 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 1960 to 2012 for all newly identified clinical questions 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, surveillance, long-term management, short-term management, short-term care, long-term care, flare progression, relapse, patient follow-up, patient compliance, contact allergen, contact allergy screen, contact allergy test, desensitization, allergen-antibody, anti-allergen, antibody, dust mites, environmental, food allergy, irritant avoidance, detergent, clothing, diet, supplement, food introduction, oil, pyridoxine, vitamin, zinc, education, complementary, alternative, herb, supplement, homeopathy, massage, acupuncture, and Chinese medicine.

A total of 2,062 abstracts were initially assessed for possible inclusion. After removal of duplicate data, 287 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 utilized by the work group in developing recommendations. The Academy's prior published guidelines on AD were evaluated, as were other current published guidelines on atopic dermatitis.²⁻⁵

The available evidence was evaluated using a unified system called the Strength of Recommendation Taxonomy (SORT) developed by editors of the 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 methodology (e.g. randomized control trial, case control, prospective/retrospective cohort, case series, etc.) and the overall focus of the study (i.e. diagnosis, treatment/prevention/screening, or prognosis) as follows:

- I. Good-quality patient-oriented evidence (i.e. 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 (i.e. evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes).

Clinical recommendations were developed based on the best available evidence tabled in the guideline. 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 those situations where documented evidence-based data is not available, we have utilized 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 five years from the date of publication, unless reaffirmed, updated, or retired at or before that time.

Definition

Atopic dermatitis 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

The often protracted nature of AD necessitates setting several long-term treatment goals: prevention of continued outbreaks, management of co-morbidities and secondary complications that arise, and minimizing adverse effects while trying to maximize positive outcomes. Clinical studies focused on more extended disease control have increased in recent years. Additional data regarding allergic co-morbidities support the need for testing or intervention, but only in particular instances. In addition to the topical and systemic approaches reviewed in earlier parts of these guidelines, multiple adjunctive and complementary modalities have been tried with varying degrees of success. Discussion of these measures and suggestions on their utilization are provided based on available evidence.

Prevention of Disease Flares

AD is characterized by periods of acute worsening (“flares”) alternating with periods of relative quiescence following treatment. The precise definition of a flare, however, differs across studies and is an ongoing area of research.⁸ For pragmatic reasons, the definitions of flare from each published paper have been accepted for this guideline.

The strategy required to minimize recurrence varies depending on the individual and his or her frequency, severity, and sites of disease. Moisturizers should be an integral part of the maintenance treatment plan given their low risk and ability to improve skin hydration; some

may also address the negative effects of epidermal barrier dysfunction.⁹⁻¹¹ Two studies have demonstrated that daily moisturizer use can lengthen the time to first flare, compared to no treatment.^{12, 13} In some cases, this strategy may be adequate and anti-inflammatory therapies reinstituted only when new eczematous lesions are noted.¹³⁻¹⁵ This is considered a reactive approach to long-term management.

However, some individuals benefit from a more proactive method, whereby topical corticosteroids (TCS) or topical calcineurin inhibitors (TCIs) are applied to previously involved and newly involved skin on a scheduled, intermittent basis and moisturizers used to all areas. Five randomized controlled trials (RCTs) with up to 4 weeks of acute disease control followed by twice weekly application of a mid-potency TCS (fluticasone propionate or methylprednisolone aceponate) for 16 to 20 weeks demonstrated a reduction in the risk of flare development and lengthening of the time to relapse or first flare, relative to vehicle.^{14, 16-19} Meta-analysis of the fluticasone studies showed a substantial magnitude of benefit (pooled relative risk of flares of 0.46 [95% CI 0.38-0.55] vs. vehicle).²⁰ Two to three times weekly application of topical tacrolimus (0.03% in children, 0.1% in adults) to previously affected sites demonstrated similar benefits over 40 to 52 weeks of use (3 RCTs, pooled relative risk of flares of 0.78 [95% CI 0.60-1.00]).²⁰⁻²³ This method of TCI use also led to a decrease in number of flares and an increase in days free of topical anti-inflammatory use, compared to vehicle. The recommendation for flare prevention is in Table II and level of evidence in Table III. Further supporting proactive treatment are histologic findings of a persistently abnormal epidermal barrier and residual low-grade inflammation at previously involved sites, even when there is little clinical evidence of involvement.²⁴

Proactive application of TCS or TCIs thus appears to be an effective strategy for AD flare prevention, but there remain unanswered questions with use. As there are no studies directly comparing the two classes of topical therapy used in this manner, it is not clear if one intervention is more effective, although meta-analysis of the vehicle-controlled trials suggested that topical fluticasone is superior to tacrolimus in preventing relapses.²⁰ Skin atrophy was not noted with scheduled, intermittent TCS use, although one study recorded a higher rate of viral and respiratory tract infections and another found increased ear, nose and throat symptoms.^{14, 16-19} Two TCS studies did not observe adrenal suppression after the 16-week maintenance period, while a third long-term safety study of up to 44 weeks of intermittent treatment noted abnormal cosyntropin stimulation testing in 2 of 44 subjects.^{14, 17, 19} The risk:benefit ratio of proactive TCS use beyond 44 weeks has not been tested, and the need for transition to TCIs or other strategies is unclear. Side effects for proactive TCI use were mainly application site reactions and in one study, skin infections and nasopharyngitis, which were also seen with the vehicle.²¹⁻²³

Continued daily use of TCIs also reduced the risk of flare in long-term studies to 12 months,^{25, 26} but efficacy compared to scheduled, intermittent dosing is unknown. Given the current black box warning against continuous TCI use (see Part 2), it seems prudent to apply them intermittently to minimize any potential long-term risks.

The optimal interval of scheduled intermittent use is not clear due to variation between studies in terms of twice weekly, three times weekly, versus two consecutive days weekly of

application. Additional variation stems from some studies applying the topical anti-inflammatory once daily and others twice daily.

Methods to identify best candidates for a proactive approach would be helpful. Some studies focused on those with moderate to severe disease based on severity scores, but many scales do not distinguish patients with very intermittent flares over a moderate or more extensive amount of body surface area from those with persistent disease at the same body sites, versus patients with rapid disease recurrence on TCS or TCI discontinuation. Skin type may also affect flare identification and there may be a need for different definitions or approaches to account for these factors.

Educational Interventions

The education of patients and caregivers is itself an important form of intervention (recommendations in Table IV, level of evidence Table III). Because AD has a complex pathogenesis and involves multiple, and sometimes rotating, therapies, it inherently requires much teaching and support to achieve and maintain good response. Increased knowledge of disease mechanisms and course, the appropriate use of therapies, and the goals of management can improve treatment adherence and lessen fears and misconceptions.²⁷ Educational methods vary greatly in scope, intensity, frequency, setting, and personnel utilized. Disease-directed teaching can be on an individual or group basis.

Formal, structured multidisciplinary educational programs (training programs, “eczema schools”) for children and adults have already been established in some countries.²⁸⁻³¹ The largest RCT to date involved 823 German children and adolescents with moderate to severe AD and their families. A six-week educational program consisting of once-weekly, two-hour sessions led by a team having dermatologic, nutritional, and psychological components resulted in decreased disease severity as measured by the SCORing Atopic Dermatitis (SCORAD) index, relative to the control group.³⁰ There have also been significant improvements in subjective assessments of severity, itching behavior, and ability to cope in groups receiving structured education.^{30, 32, 33} Increased adaptive use of medication based on AD severity has also been demonstrated.³³ Such formal training programs have the strongest supportive evidence, but do require significant personnel and financial resources. Comparison between programs is difficult because the content is heterogeneous and outcome measures vary greatly between studies.³⁴

As physician time during clinic visits is often limited, workshops and nurse-led educational sessions can be of benefit to patients, improving knowledge and utilization of topical treatments.³⁵⁻⁴¹ One systematic review found increased patient satisfaction as a result of longer consultation and similar health outcomes to doctor-led care.³⁷ Other educational methods include parental education via standardized video instruction, which in one RCT was more effective than direct parental teaching in improving AD symptoms, and in a second RCT, led to greater improvements in severity score and AD knowledge than a written pamphlet.^{41, 42} Furthermore, video-assisted approaches were less time consuming.⁴¹

Written action plans also assist in reinforcing teachings.⁴³ Practitioners should be aware of educator and lay-led management resources, such as the educational information and

support groups provided by organizations such as the National Eczema Association (<http://nationaleczema.org/>). These facilitate communication and networking between affected patients and families, although their effects on AD outcomes have not been formally tested.

Psychological interventions have also been utilized to help with coping with AD and include autogenic training, biofeedback, brief dynamic psychotherapy, cognitive-behavioral therapy, habit reversal behavioral therapy, and a stress management program. Most of these adjunctive therapies are limited to case series, and with different outcome measures utilized that preclude comparison.⁴⁴ One RCT of children receiving hypnotherapy or biofeedback showed a statistically significant reduction in the severity of surface damage and lichenification, but not in erythema, compared to the control group.³⁴

Co-Existing Allergic Disease and Allergy Testing

Patients and caregivers often seek allergy assessment to find a single cause or trigger which could be eliminated to obtain “cure” or at least reduce the need for treatment. However, the role of allergens in eliciting and maintaining AD skin lesions is complex, further complicated by challenges in determining clinical relevance and their importance relative to other factors. Foods and inhalant/aeroallergens are common concerns, and along with contact allergens, are the most relevant for discussion.

Food Allergies

A fair number of children and a much smaller percentage of adult patients with AD have food allergies, particularly those of younger age and with more severe disease.⁴⁵ The exact impact of food exposure on the course of AD remains unclear. Asthma is a stronger risk factor for food allergy than AD.

A true allergy is defined as “an adverse health event that results from stimulation of a specific immune response that occurs reproducibly on exposure.”⁴⁶ Thus, reproducible clinical symptoms or signs after food exposure/ingestion are necessary to diagnose food allergy, and broad panel allergy testing independent of a history of a reaction to foods is not recommended. Positive test results may reflect sensitization, associated with IgE reactivity, but have poor correlation with clinical allergic responses.^{47, 48} Moreover, exposure to allergenic foods may or may not induce eczematous dermatitis (a delayed reaction typically 6 to 48 hours later), but more often gives immediate/type I, non-dermatitic reactions (usually within 2 hours) that include local or generalized urticaria, flushing, or itch. Food allergy may also present as gastrointestinal or respiratory symptoms, and at times, as anaphylaxis. It is therefore important not only to establish presence of a true food allergy, but also to determine if the food allergy is exacerbating AD, either directly via immune cell activation or indirectly via increased pruritus, or is instead a co-existing condition with non-AD manifestations.

The National Institute of Allergy and Infectious Diseases (NIAID) Food Allergy Expert Panel suggests consideration of limited food allergy testing (of cow's milk, eggs, wheat, soy, and peanut) if a child less than 5 years of age has moderate to severe AD and: i) persistent disease in spite of optimized management and topical therapy; ii) a reliable history of an

immediate allergic reaction after ingestion of a specific food; or iii) both.⁴⁶ While food allergy is less common in older age groups, when suspected, the choice of food for testing should be made according to the clinical history and to the most prevalent allergies in a given population. Tree nuts, shellfish, and fish become relevant in subsequent childhood years.⁴⁸ In older children, adolescents, and adults, pollen-related food allergy should be taken into account; for example, those with birch pollen allergy may develop itching in their mouth with exposure to apples, celery, carrots, and hazelnuts.⁴⁹

Tests often performed for evaluation include skin prick testing (SPT) and serum specific IgE level determination, which assess for immediate/type I hypersensitivity reactions. SPT is an *in vivo* test based on introducing allergen extracts which bind to specific IgE antibodies on mast cells, causing release of histamine and other mediators that give rapid formation of a wheal and flare. Food-specific IgE levels may be measured in the serum by *in vitro* assays such as radioallergen sorbent testing (RAST) or immunoCAP testing. In cases of extensive eczematous lesions, prominent dermatographism, or recent use of oral antihistamines, specific IgE measurement may be preferable over SPT. With both tests, the negative predictive value is high (>95%), while the specificity and positive predictive value are low (40 to 60%).⁵⁰⁻⁵² Negative test results are helpful to rule out food allergy, but positive results only signify sensitization and require clinical correlation and confirmation to establish presence of allergic disease and the exact type of allergic response. Higher specific IgE levels and larger wheal sizes (>8–10 mm) are associated with a greater likelihood of reaction on challenge.⁴⁶ Measuring total serum IgE levels alone, or to compare with allergen-specific levels, is not helpful in determining food allergy.^{46, 53}

In recent years, atopy patch tests (APT) have been introduced to assess for type IV hypersensitivity/eczematous reactions. These involve applying custom-made food material for 48 to 72 hours to the back using 8-12 mm test chambers. Food APT are not commonly used in evaluation of patients in North America, but have been the subject of investigation in Europe. One European multicenter study showed that APT tests have a higher specificity than SPT or specific IgE, particularly in the case of wheat, while other studies noted that APT could not predict food hypersensitivity beyond that of SPT or specific IgE testing.⁵⁴⁻⁵⁷ These conflicting findings might be explained by the sometimes difficult interpretation of APT due to non-specific reactions. In addition, while AD patients demonstrate more reactivity than healthy controls, results do not necessarily correlate with disease severity or clinical outcome⁵⁸⁻⁶⁰ and thus, APT are not recommended for routine use at this time.

Positive skin or blood tests ideally need to be verified by controlled food challenges. The gold standard test for diagnosing food allergy is a double-blind, placebo-controlled oral food challenge (DBPCFC).⁴⁶ In this case, testing is performed after a washout period. Potential allergenic foods and placebo are given in a randomized, titrated fashion, and both the patient and observer are blinded to the test food. As this may not always be practical, open-label or single-blind oral food challenges are more commonly used in clinical practice to screen for reactions. Such challenges should be performed under the guidance of well-trained medical personnel and with emergency equipment available. Another alternative is careful assessment of the effects of a food elimination diet carried out in the absence of other

exacerbating factors. Avoidance diets should be cautiously undertaken, however, and are further discussed below (see Dietary Interventions).

Even if food allergies are present, effective treatment for AD is still centered on good skin care and topical therapies. In addition, children with clinically significant food allergy will often develop tolerance over time to milk, egg, soy, and wheat, so these allergens should be re-tested with age.⁶¹ Food allergies in adults can reflect persistence of childhood allergies or *de novo* sensitization to allergens encountered after childhood. Although data are limited, there is a suggestion that food allergies starting in adult life tend to be persistent.⁶²

Inhalant/Aeroallergens

In contrast to food allergy, reactivity to aeroallergens increases with age. Common aeroallergens include house dust mites, pollens, animal dander, and fungi and higher rates of sensitization are noted in those with moderate to severe AD.⁶³ As with foods, true allergy to aeroallergens requires demonstration of an adverse health event that is reproducible on exposure, along with discernment of the clinical reaction. The exact role of aeroallergens in AD pathogenesis is controversial, as inhalation may induce release of pro-inflammatory cytokines in the skin of sensitized patients, but avoidance measures have not consistently helped (discussed under Environmental Modifications).^{64, 65} Skin contact with aeroallergens triggers eczematous skin lesions in some individuals but not others (5-45% positivity, depending on the allergen)^{54, 66-68}

The diagnosis of allergy to an aeroallergen is based on a sequential workup and demonstration of clinical relevance. History can be helpful to identify pollens or animal dander as potential triggers, such as seasonal flares or exacerbation of AD lesions after contact. Aeroallergens may also be suspected if the dermatitis is more severe on exposed surfaces of the face, neck, arms, legs, and “V” area of the chest. In a second step, SPT or measurement of specific IgE antibodies can be performed to detect sensitization.^{68, 69}

APT with epicutaneous application of aeroallergens on uninvolved atopic skin has also been used for testing. Positive eczematoid reactions have been observed in 30 to 50% of patients with AD, but only rarely in patients with respiratory allergy and healthy volunteers.^{54, 70} Some noted APT to have a higher specificity but lower sensitivity than SPT or specific IgE for potential aeroallergen triggers, while Kerschenlohr and colleagues reported positive APT in patients with AD even in the absence of detectable aeroallergen-specific serum IgE and with negative SPT results.^{71, 72} Some have suggested APT use when there is a high suspicion of aeroallergen-related symptoms or if there is severe and/or persistent AD with unknown triggering factors. The major disadvantage with APT, however, is the variability of methods and interpretation of results among investigators, along with the lack of a commercially available product. Standardization of the procedure has been proposed, but is hampered by the lack of a comparator gold standard test that establishes the diagnosis of aeroallergen-induced or exacerbated dermatitis.⁶⁰

Allergic Contact Dermatitis

Increasingly recognized in individuals with AD is the high prevalence of allergic contact dermatitis (ACD), a type IV/delayed-type hypersensitivity reaction to small environmental chemicals (haptens or prehapens) in direct contact with the skin. These bind to epidermal carrier proteins to form complete antigens, cause sensitization, and induce an inflammatory reaction on subsequent exposure. Because ACD manifests as eczematous lesions, it is often clinically indistinguishable from AD and as discussed in Part 1, should be considered both as an alternative diagnosis to AD and as a concomitant condition. Recent studies show that ACD is at least as common in patients with AD as in the general population (6-60% of subjects depending on the study).⁷³⁻⁷⁵

The most common contact allergens in AD patients include nickel, neomycin, fragrance, formaldehyde and other preservatives, lanolin, and rubber chemicals.^{76, 77} A small subset of patients may even develop ACD to some topical corticosteroids and can pose a diagnostic dilemma for the clinician. Diagnosis is by patch testing, whereby suspected allergens are placed on unaffected skin, typically the back, for 48 hours. Presence of a reaction should be assessed at the time of initial patch removal and again at a later time point, up to 7 days after application, for delayed reactions. Patch testing should be considered in cases where a history and/or physical exam is suggestive of ACD, such as disease aggravated by topical medications or emollients or patterns that reflect application of, or exposure to, a consistent item, such as marked facial and/or eyelid involvement, increased severity at the flexures of the neck, and vesicular lesions on the dorsal hands and fingertips (recommendation in Table V, level of evidence in Table III). Testing may also be considered where there is an unusual and atypical distribution of lesions for AD (e.g. on the sides of the feet), if there is later onset of disease or new significant worsening, if there is no family history of atopy, and in those with persistent/recalcitrant disease not responding to standard AD therapies.^{78, 79} Even some cases of generalized dermatitis may involve ACD, such as to fragrances, preservatives, cleansers, and textiles⁸⁰, but are a challenge to recognize as well as to test if there is little uninvolved skin. The sensitivity of patch testing ranges from 60-80% in reports.^{81, 82} Positive patch tests only indicate contact sensitization and need demonstrated relevance to the patient's active dermatitis and sometimes confirmation by repeat open application testing of products containing the allergen that have been in contact with the patient.^{83, 84} Avoidance of the suspected allergen with resolution of the corresponding dermatitis confirms the diagnosis of ACD.

In summary, allergens may be pertinent to some AD patients but require a detailed history, careful evaluation, and correlation of allergy test results to determine clinical relevance. It is extremely rare to find one allergen responsible for AD, which is a complex multifactorial disease in which non-allergic factors, such as climate and secondary infection, may also be implicated.

Dietary Interventions

Food Elimination/Avoidance Diets

Large numbers of patients with AD, particularly children, are started on empiric food elimination/avoidance diets. However, there is a frequent misattribution of AD flares to food-related issues. Although food allergies may co-exist and represent important triggers in a small subset of individuals with AD (usually those with moderate to severe disease), the true frequency of food allergies causing an isolated flare of disease is probably low.⁸⁵

Elimination diets should not be initiated based on presence of AD or a suspicious history alone.⁸⁶ A 2008 Cochrane Review concluded that there may be some benefit to an egg-free diet in infants with suspected egg allergy who also have positive specific IgE to eggs, but other exclusion diets (milk-free, elemental, few-foods diets) were not found to be efficacious in unselected AD populations.⁸⁷ If allergy is suspected as a trigger of AD, a food diary recording symptoms and intake can be helpful in identifying a specific food.^{88, 89} If there is consistent correlation of symptoms (with or without positive allergy testing), a diagnostic elimination diet for up to 4 to 6 weeks with the suspected food item(s) may be initiated. If the individual's AD remains stable or even increases in severity, it is unlikely that the food is a relevant AD trigger and further testing is not necessary. If there is an improvement of the symptoms during a diagnostic elimination diet, an oral food challenge should be performed under the guidance of an allergist, as the skin improvement may be coincidental or reflect a placebo effect.^{56, 88} If a patient has positive allergy tests but no history of symptomatic food allergy, review with an allergist regarding the issue of true versus false positive tests (allergy vs. only sensitization) is warranted, along with discussion of benefits and downsides of formal food challenge. A retrospective study by Fleischer et al. on the outcome of oral food challenges in children with AD following elimination diets primarily based on sensitization demonstrated that 84 to 93% of the avoided foods could be returned to the diet and could be tolerated.⁹⁰

Multiple dietary restrictions and long-term dietary avoidance should only be undertaken with documented, clinically relevant food allergies.⁴⁶ Excessively restrictive diets, especially in atopic children, have led to weight loss, poor growth, calcium deficiency, hypovitaminosis, and kwashiorkor.^{91, 92} Proper medical supervision, nutritional counseling from a dietician, and supplementation should be included if elimination/avoidance diets are pursued for any prolonged period of time. Even in those individuals with clinically relevant food allergy, avoidance diets are generally helpful to avoid the effects of IgE-mediated/ immediate reactions but are unlikely to affect the course of AD.^{46, 87} A summary of these recommendations is shown in Table VI, with the level of evidence in Table III.

Probiotics/Prebiotics

The study of probiotics for AD management stems from the finding that the intestinal microbiota is different in those with and without AD.⁹³ Probiotics are live microorganisms that modify the overall composition of this microbiota and potentially modulate the host immune response. However, studies have found limited evidence to support their use as a treatment for established AD.⁹⁴ A Cochrane review of 12 RCTs involving 785 children (age

3 months to 13 years) included a variety of probiotic strains and found no significant differences in symptoms or disease severity compared to placebo.⁹⁵ On meta-analysis, the effect of probiotics, even if present, was small and likely not clinically noticeable (statistically significant SCORAD decrease of 2.47 points, 95% CI -4.72, -0.21, $p=0.03$, noted only after correcting for baseline severity differences; two studies could not be pooled with this method). Three studies included prebiotics, specialized plant fibers to help nourish the bacteria, but also with mixed effects.⁹⁶⁻⁹⁸ Pro/prebiotic use cannot be recommended at this time (level of evidence in Table III).

Other dietary supplements

A deficiency of essential fatty acids in the skin has been proposed as having a role in AD. Fish oils are particularly rich in n-3 fatty acids, and are suggested to compete with n-6 fatty acids in a manner that reduces the inflammatory components of AD. There is, however, little supportive data for either.⁹⁹⁻¹⁰¹ Evening primrose oil and borage oil have been tried orally due to their gamma-linolenic acid content, considered to have anti-inflammatory properties. Several RCTs of evening primrose oil have had mixed results, with the majority of data finding no benefit.¹⁰²⁻¹⁰⁶ Two RCTs evaluating the use of oral borage oil in the treatment of atopic dermatitis did not show improvement in key outcomes compared with placebo.^{107, 108}

Vitamins and minerals have also been tried but none with adequate data to support their use.¹⁰⁹ Multivitamins have not been tested alone; zinc was not helpful in one RCT.¹¹⁰ Some studies suggest a mild positive effect for vitamin D and E supplementation, but larger, well-controlled trials are warranted prior to any formal recommendations.¹¹¹⁻¹¹³ Topical B12 cream was helpful in one 4-week blinded study but has not been tested further. Vitamin B6/pyridoxine supplementation did not make any difference in one 4-week, placebo-controlled study.¹¹⁴

Environmental Modifications

Environmental modifications mainly stem from expert/consensus recommendations as there are few well-controlled studies. General recommendations are to avoid known mechanical and chemical irritants, such as wool, acids, bleaches, and solvents, and any clear triggers/exacerbants particular to the individual (e.g. excessive heat in some cases).

A large majority of studies testing environmental modifications have centered on house dust mite (HDM) interventions. Sensitization to HDM is commonly demonstrated in AD patients and exposure can also cause worsening of allergic rhinitis and asthma in sensitized individuals.¹¹⁵ The evidence is limited, however, to support the routine use of HDM avoidance measures. Normal cleaning measures (such as washing bedding weekly, vacuuming frequently) only provide small decreases in HDM allergen present in the room. While covers may reduce levels of HDM and sensitization levels, studies have not shown improvement in AD severity, particularly in adults.¹¹⁵⁻¹¹⁹ One study did show improvement in children and greater effect in those most severely affected.¹¹⁶ As a result, the current workgroup notes that in patients who are sensitized to HDM and whose AD is uncontrolled, the clinician could consider recommending a house dust mite cover for the pillow and mattress.

There is a paucity of clinical studies on specific laundering techniques (such as double rinsing and other methods), detergents, or other laundry products and their impact on AD management.^{120, 121} Use of ion-exchange water softeners for bathing and laundering clothing was not of benefit in a large RCT.¹²² Low pH products may be better due to potentially fewer negative effects on the skin barrier, while botanical products (plant derived extracts and herbs) may not be as they have irritant contact dermatitis (ICD) and ACD risks.^{123, 124} Fabric softener with perfumes can cause irritation^{125, 126}, but there is a small amount of data indicating that softened fabrics might help due to reduced frictional irritation.¹²⁷

Smooth clothing and avoidance of irritating fabrics and fibers are favored to minimize skin irritation. There are a small number of controlled studies indicating that specialty silk garments may improve severity scores, although at this time it is not clear whether silk and specialty silks impregnated with antibacterial agents provide significantly more improvement compared to soft cotton.¹²⁸⁻¹³⁰ Silver impregnated clothing can decrease *Staphylococcus aureus* density, but did not improve disease severity more than soft cotton in one study.¹³¹ More research into this area is warranted before recommendations can be offered regarding specialized clothing fabrics, which do have higher cost.

Other Allergen-Based Interventions

Allergen-specific immunotherapies have been used in the treatment of asthma and allergic rhinitis and are now being tested for AD management. Preliminary studies on sublingual immunotherapy for dust mites demonstrated modest positive results, which may be more evident in those with milder AD.^{132, 133} Nine to twelve months of immunotherapy were needed to observe the beneficial effect. The present evidence does not warrant routine recommendation of sublingual immunotherapy for dust mite sensitized atopic dermatitis patients. A series of small prospective studies on injection immunotherapy for HDM also had positive results, although there was also one negative study.¹³⁴⁻¹⁴⁰ Injection immunotherapy for dust mite sensitized patients also cannot be routinely recommended at this time. Studies examining immunotherapy for other aeroallergens are even more limited in number (less than five RCTs), precluding recommendation for use.

Complementary Therapies

At this time, there is little data to support the majority of complementary therapies tried for AD management. Chinese herbal therapy (or Traditional Chinese Medicine, TCM) has been the most extensively studied. While it may have some benefit for AD lesions, the results from RCTs of TCM taken orally are conflicting, and reports of serious hepatotoxicity raise potential safety concerns.^{141, 142} Some herbal creams have been found to be contaminated with topical corticosteroids.¹⁴³ The individualized and dynamic nature of this intervention (e.g. a different herb is added or subtracted depending on the patient) also poses challenges to performing controlled studies. Acupuncture alone or in conjunction with TCM decreases signs and symptoms of AD, but the evidence is confined to small studies of limited quality.^{144, 145}

Massage therapy may improve symptoms as well as associated patient and parental anxiety levels.^{146, 147} While it is a quite safe intervention, studies to date are small and of limited quality, precluding recommendation at this time. Other complementary therapies lacking sufficient evidence include: aromatherapy (no studies), homeopathy (one positive prospective study), naturopathy (no studies), acupressure (one study), and autologous blood injections (one study).¹⁴⁸⁻¹⁵⁰

Gaps in Research

In review of the currently available highest level of evidence, the expert work group acknowledges that while multiple studies have been performed on prevention of flares and the use of adjunctive therapies and approaches, much has yet to be learned. Significant gaps in research were identified, including but not limited to: methodological research on the best instruments for defining disease flares in long-term AD trials; comparative studies to decide on best agents for long-term maintenance therapy; increased long-term safety data for intermittent use of TCS and TCIs; high quality research on the role of foods and aeroallergens in AD with an emphasis on clear morphologic description of cutaneous reactions; and trials assessing outcomes of ACD testing and avoidance measures in AD patients. Additional large, well-controlled trials are needed to further test the effects of adjunctive treatments showing positive data, including vitamins D and E, specialized clothing fabrics, immunotherapy for highly dust mite sensitized patients with persistent AD, and complementary therapies.

Acknowledgments

We thank Melinda Jen, MD, Michael Osofsky, MD, Kathleen Muldowney, MLS, Charniel 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 (NIH)/National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) research career development grant (K23AR060274). The content is solely the responsibility of the authors and does not necessarily represent the official views of NIAMS or NIH.

Funding Source: None

References

1. 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 dermatology*. 2011; 11:10. [PubMed: 21592376]
2. 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. [PubMed: 14988682]
3. 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. [PubMed: 22805051]
4. 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. [PubMed: 22813359]

5. 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. [PubMed: 23374261]
6. 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. *The Journal of the American Board of Family Practice/American Board of Family Practice*. 2004; 17:59–67. [PubMed: 15014055]
7. American Academy of Dermatology. [Accessed November 2011] Administrative Regulations; Evidence Based Clinical Practice Guidelines. Available at: www.aad.org/Forms/Policies/Uploads/AR/AR%20-%20Evidence-Based%20Clinical%20Guideline.pdf
8. Langan SM, Schmitt J, Williams HC, Smith S, Thomas KS. How are eczema “flares” defined? A systematic review and recommendation for future studies. *Br J Dermatol*. 2013
9. Lodén M, Andersson AC, Lindberg M. Improvement in skin barrier function in patients with atopic dermatitis after treatment with a moisturizing cream (Canoderm). *Br J Dermatol*. 1999; 140:264–7. [PubMed: 10233220]
10. Breternitz M, Kowatzki D, Langenauer M, Elsner P, Fluhr JW. Placebo-controlled, double-blind, randomized, prospective study of a glycerol-based emollient on eczematous skin in atopic dermatitis: biophysical and clinical evaluation. *Skin Pharmacol Physiol*. 2008; 21:39–45. [PubMed: 18025807]
11. Chamlin SL, Kao J, Frieden IJ, Sheu MY, Fowler AJ, Fluhr JW, et al. Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity. *J Am Acad Dermatol*. 2002; 47:198–208. [PubMed: 12140465]
12. Szczepanowska J, Reich A, Szepietowski JC. Emollients improve treatment results with topical corticosteroids in childhood atopic dermatitis: a randomized comparative study. *Pediatr Allergy Immunol*. 2008; 19:614–8. [PubMed: 18208463]
13. Wiren K, Nohlgard C, Nyberg F, Holm L, Svensson M, Johannesson A, et al. Treatment with a barrier-strengthening moisturizing cream delays relapse of atopic dermatitis: a prospective and randomized controlled clinical trial. *J Eur Acad Dermatol Venereol*. 2009; 23:1267–72. [PubMed: 19508310]
14. Hanifin J, Gupta AK, Rajagopalan R. Intermittent dosing of fluticasone propionate cream for reducing the risk of relapse in atopic dermatitis patients. *Br J Dermatol*. 2002; 147:528–37. [PubMed: 12207596]
15. Siegfried E, Korman N, Molina C, Kianifard F, Abrams K. Safety and efficacy of early intervention with pimecrolimus cream 1% combined with corticosteroids for major flares in infants and children with atopic dermatitis. *J Dermatolog Treat*. 2006; 17:143–50. [PubMed: 16854753]
16. Berth-Jones J, Damstra RJ, Golsch S, Livden JK, Van Hootehem O, Allegra F, et al. Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. *BMJ*. 2003; 326:1367. [PubMed: 12816824]
17. Glazenburg EJ, Wolkerstorfer A, Gerretsen AL, Mulder PG, Oranje AP. Efficacy and safety of fluticasone propionate 0.005% ointment in the long-term maintenance treatment of children with atopic dermatitis: differences between boys and girls? *Pediatr Allergy Immunol*. 2009; 20:59–66. [PubMed: 18298423]
18. Peserico A, Stadtler G, Sebastian M, Fernandez RS, Vick K, Bieber T. Reduction of relapses of atopic dermatitis with methylprednisolone aceponate cream twice weekly in addition to maintenance treatment with emollient: a multicentre, randomized, double-blind, controlled study. *Br J Dermatol*. 2008; 158:801–7. [PubMed: 18284403]
19. Van Der Meer JB, Glazenburg EJ, Mulder PG, Eggink HF, Coenraads PJ. The management of moderate to severe atopic dermatitis in adults with topical fluticasone propionate. The Netherlands Adult Atopic Dermatitis Study Group. *Br J Dermatol*. 1999; 140:1114–21. [PubMed: 10354080]
20. Schmitt J, von Kobyletzki L, Svensson A, Apfelbacher C. Efficacy and tolerability of proactive treatment with topical corticosteroids and calcineurin inhibitors for atopic eczema: systematic review and meta-analysis of randomized controlled trials. *Br J Dermatol*. 2011; 164:415–28. [PubMed: 20819086]

21. Breneman D, Fleischer AB Jr, Abramovits W, Zeichner J, Gold MH, Kirsner RS, et al. Intermittent therapy for flare prevention and long-term disease control in stabilized atopic dermatitis: a randomized comparison of 3-times-weekly applications of tacrolimus ointment versus vehicle. *J Am Acad Dermatol*. 2008; 58:990–9. [PubMed: 18359127]
22. Thaci D, Chambers C, Sidhu M, Dorsch B, Ehlken B, Fuchs S. Twice-weekly treatment with tacrolimus 0.03% ointment in children with atopic dermatitis: clinical efficacy and economic impact over 12 months. *J Eur Acad Dermatol Venereol*. 2010; 24:1040–6. [PubMed: 20158589]
23. Wollenberg A, Reitamo S, Girolomoni G, Lahfa M, Ruzicka T, Healy E, et al. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. *Allergy*. 2008; 63:742–50.
24. Suarez-Farinas M, Tintle SJ, Shemer A, Chiricozzi A, Nogales K, Cardinale I, et al. Nonlesional atopic dermatitis skin is characterized by broad terminal differentiation defects and variable immune abnormalities. *J Allergy Clin Immunol*. 2011; 127:954–64 e1–4. [PubMed: 21388663]
25. Kang S, Lucky AW, Pariser D, Lawrence I, Hanifin JM. Long-term safety and efficacy of tacrolimus ointment for the treatment of atopic dermatitis in children. *J Am Acad Dermatol*. 2001; 44:S58–64. [PubMed: 11145796]
26. Kapp A, Papp K, Bingham A, Folster-Holst R, Ortonne JP, Potter PC, et al. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. *J Allergy Clin Immunol*. 2002; 110:277–84. [PubMed: 12170269]
27. Smith SD, Hong E, Fearn S, Blaszczyński A, Fischer G. Corticosteroid phobia and other confounders in the treatment of childhood atopic dermatitis explored using parent focus groups. *Australas J Dermatol*. 2010; 51:168–74. [PubMed: 20695854]
28. Grillo M, Gassner L, Marshman G, Dunn S, Hudson P. Pediatric atopic eczema: the impact of an educational intervention. *Pediatr Dermatol*. 2006; 23:428–36. [PubMed: 17014636]
29. 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. [PubMed: 19250397]
30. Staab D, Diepgen TL, Fartasch M, Kupfer J, Lob-Corzilius T, Ring J, et al. Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: multicentre, randomised controlled trial. *BMJ*. 2006; 332:933–8. [PubMed: 16627509]
31. Lambert J, Bostoen J, Geusens B, Bourgois J, Boone J, De Smedt D, et al. A novel multidisciplinary educational programme for patients with chronic skin diseases: Ghent pilot project and first results. *Archives of dermatological research*. 2011; 303:57–63. [PubMed: 20842368]
32. Kupfer J, Gieler U, Diepgen TL, Fartasch M, Lob-Corzilius T, Ring J, et al. Structured education program improves the coping with atopic dermatitis in children and their parents—a multicenter, randomized controlled trial. *Journal of psychosomatic research*. 2010; 68:353–8. [PubMed: 20307702]
33. Staab D, von Rueden U, Kehrt R, Erhart M, Wenninger K, Kamtsiuris P, et al. Evaluation of a parental training program for the management of childhood atopic dermatitis. *Pediatr Allergy Immunol*. 2002; 13:84–90. [PubMed: 12000479]
34. Ersser SJ, Latter S, Sibley A, Satherley PA, Welbourne S. Psychological and educational interventions for atopic eczema in children. *Cochrane Database Syst Rev*. 2007:CD004054. [PubMed: 17636745]
35. Cork MJ, Britton J, Butler L, Young S, Murphy R, Keohane SG. Comparison of parent knowledge, therapy utilization and severity of atopic eczema before and after explanation and demonstration of topical therapies by a specialist dermatology nurse. *Br J Dermatol*. 2003; 149:582–9. [PubMed: 14510993]
36. Gradwell C, Thomas KS, English JS, Williams HC. A randomized controlled trial of nurse follow-up clinics: do they help patients and do they free up consultants' time? *Br J Dermatol*. 2002; 147:513–7. [PubMed: 12207593]
37. Moore E, Williams A, Manias E, Varigos G. Nurse-led clinics reduce severity of childhood atopic eczema: a review of the literature. *Br J Dermatol*. 2006; 155:1242–8. [PubMed: 17107396]

38. Moore EJ, Williams A, Manias E, Varigos G, Donath S. Eczema workshops reduce severity of childhood atopic eczema. *Australas J Dermatol.* 2009; 50:100–6. [PubMed: 19397561]
39. Broberg A, Kalimo K, Lindblad B, Swanbeck G. Parental education in the treatment of childhood atopic eczema. *Acta Derm Venereol.* 1990; 70:495–9. [PubMed: 1981422]
40. Chinn DJ, Poyner T, Sibley G. Randomized controlled trial of a single dermatology nurse consultation in primary care on the quality of life of children with atopic eczema. *Br J Dermatol.* 2002; 146:432–9. [PubMed: 11952543]
41. Niebel G, Kallweit C, Lange I, Folster-Holst R. Direct versus video-aided parent education in atopic eczema in childhood as a supplement to specialty physician treatment. A controlled pilot study. *Hautarzt.* 2000; 51:401–11. [PubMed: 10907154]
42. Armstrong AW, Kim RH, Idriss NZ, Larsen LN, Lio PA. Online video improves clinical outcomes in adults with atopic dermatitis: a randomized controlled trial. *J Am Acad Dermatol.* 2011; 64:502–7. [PubMed: 21236514]
43. Ntuen E, Taylor SL, Kinney M, O'Neill JL, Krowchuk DP, Feldman SR. Physicians' perceptions of an eczema action plan for atopic dermatitis. *J Dermatolog Treat.* 2010; 21:28–33. [PubMed: 19968578]
44. Chida Y, Steptoe A, Hirakawa N, Sudo N, Kubo C. The effects of psychological intervention on atopic dermatitis. A systematic review and meta-analysis. *International archives of allergy and immunology.* 2007; 144:1–9. [PubMed: 17449959]
45. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics.* 1998; 101:E8. [PubMed: 9481027]
46. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol.* 2010; 126:S1–58. [PubMed: 21134576]
47. Oranje AP, Bruynzeel DP, Stenveld HJ, Dieges PH. Immediate- and delayed-type contact hypersensitivity in children older than 5 years with atopic dermatitis: a pilot study comparing different tests. *Pediatr Dermatol.* 1994; 11:209–15. [PubMed: 7971554]
48. Sicherer SH, Sampson HA. Food hypersensitivity and atopic dermatitis: pathophysiology, epidemiology, diagnosis, and management. *J Allergy Clin Immunol.* 1999; 104:S114–22. [PubMed: 10482862]
49. Breuer K, Wulf A, Constien A, Tetau D, Kapp A, Werfel T. Birch pollen-related food as a provocation factor of allergic symptoms in children with atopic eczema/dermatitis syndrome. *Allergy.* 2004; 59:988–94. [PubMed: 15291908]
50. Bock SA, Lee WY, Remigio L, Holst A, May CD. Appraisal of skin tests with food extracts for diagnosis of food hypersensitivity. *Clin Allergy.* 1978; 8:559–64. [PubMed: 81723]
51. Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind, placebo-controlled food challenges in children with atopic dermatitis. *J Allergy Clin Immunol.* 1984; 74:26–33. [PubMed: 6547461]
52. Lemon-Mule H, Nowak-Wegrzyn A, Berin C, Knight AK. Pathophysiology of food-induced anaphylaxis. *Curr Allergy Asthma Rep.* 2008; 8:201–8. [PubMed: 18589838]
53. Mehl A, Verstege A, Staden U, Kulig M, Nocon M, Beyer K, et al. Utility of the ratio of food-specific IgE/total IgE in predicting symptomatic food allergy in children. *Allergy.* 2005; 60:1034–9. [PubMed: 15969684]
54. Darsow U, Laifaoui J, Kerschenlohr K, Wollenberg A, Przybilla B, Wuthrich B, et al. The prevalence of positive reactions in the atopy patch test with aeroallergens and food allergens in subjects with atopic eczema: a European multicenter study. *Allergy.* 2004; 59:1318–25. [PubMed: 15507101]
55. Hansen TK, Host A, Bindslev-Jensen C. An evaluation of the diagnostic value of different skin tests with egg in clinically egg-allergic children having atopic dermatitis. *Pediatr Allergy Immunol.* 2004; 15:428–34. [PubMed: 15482518]
56. Breuer K, Heratizadeh A, Wulf A, Baumann U, Constien A, Tetau D, et al. Late eczematous reactions to food in children with atopic dermatitis. *Clin Exp Allergy.* 2004; 34:817–24. [PubMed: 15144477]

57. Osterballe M, Andersen KE, Bindslev-Jensen C. The diagnostic accuracy of the atopy patch test in diagnosing hypersensitivity to cow's milk and hen's egg in unselected children with and without atopic dermatitis. *J Am Acad Dermatol*. 2004; 51:556–62. [PubMed: 15389190]
58. Samochocki Z, Owczarek W, Zabielski S. Can atopy patch tests with aeroallergens be an additional diagnostic criterion for atopic dermatitis? *Eur J Dermatol*. 2006; 16:151–4. [PubMed: 16581566]
59. Keskin O, Tuncer A, Adalioglu G, Sekerel BE, Sackesen C, Kalayci O. Evaluation of the utility of atopy patch testing, skin prick testing, and total and specific IgE assays in the diagnosis of cow's milk allergy. *Ann Allergy Asthma Immunol*. 2005; 94:553–60. [PubMed: 15945559]
60. Lipozencic J, Wolf R. The diagnostic value of atopy patch testing and prick testing in atopic dermatitis: facts and controversies. *Clinics in dermatology*. 2010; 28:38–44. [PubMed: 20082949]
61. Shek LP, Soderstrom L, Ahlstedt S, Beyer K, Sampson HA. Determination of food specific IgE levels over time can predict the development of tolerance in cow's milk and hen's egg allergy. *J Allergy Clin Immunol*. 2004; 114:387–91. [PubMed: 15316521]
62. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of seafood allergy in the United States determined by a random telephone survey. *J Allergy Clin Immunol*. 2004; 114:159–65. [PubMed: 15241360]
63. Schafer T, Heinrich J, Wjst M, Adam H, Ring J, Wichmann HE. Association between severity of atopic eczema and degree of sensitization to aeroallergens in schoolchildren. *J Allergy Clin Immunol*. 1999; 104:1280–4. [PubMed: 10589013]
64. Tupker RA, De Monchy JG, Coenraads PJ, Homan A, van der Meer JB. Induction of atopic dermatitis by inhalation of house dust mite. *J Allergy Clin Immunol*. 1996; 97:1064–70. [PubMed: 8626983]
65. Tuft L, Heck VM. Studies in atopic dermatitis. IV. Importance of seasonal inhalant allergens, especially ragweed. *J Allergy*. 1952; 23:528–40. [PubMed: 12990302]
66. Krupa Shankar DS, Chakravarthi M. Atopy patch testing. *Indian J Dermatol Venereol Leprol*. 2008; 74:467–70. [PubMed: 19052405]
67. Michel S, Yawalkar N, Schnyder B, Fischer B, Helbling A. Eczematous skin reaction to atopy patch testing with cockroach in patients with atopic dermatitis. *J Investig Allergol Clin Immunol*. 2009; 19:173–9.
68. Darsow U, Vieluf D, Ring J. Evaluating the relevance of aeroallergen sensitization in atopic eczema with the atopy patch test: a randomized, double-blind multicenter study. Atopy Patch Test Study Group. *J Am Acad Dermatol*. 1999; 40:187–93. [PubMed: 10025743]
69. Scalabrin DM, Bavbek S, Perzanowski MS, Wilson BB, Platts-Mills TA, Wheatley LM. Use of specific IgE in assessing the relevance of fungal and dust mite allergens to atopic dermatitis: a comparison with asthmatic and nonasthmatic control subjects. *J Allergy Clin Immunol*. 1999; 104:1273–9. [PubMed: 10589012]
70. Seidenari S, Giusti F, Pellacani G, Bertoni L. Frequency and intensity of responses to mite patch tests are lower in nonatopic subjects with respect to patients with atopic dermatitis. *Allergy*. 2003; 58:426–9. [PubMed: 12752330]
71. Darsow U, Lubbe J, Taieb A, Seidenari S, Wollenberg A, Calza AM, et al. Position paper on diagnosis and treatment of atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2005; 19:286–95. [PubMed: 15857453]
72. Kerschenlohr K, Darsow U, Burgdorf WH, Ring J, Wollenberg A. Lessons from atopy patch testing in atopic dermatitis. *Curr Allergy Asthma Rep*. 2004; 4:285–9. [PubMed: 15175142]
73. Jacob SE, Yang A, Herro E, Zhang C. Contact allergens in a pediatric population: association with atopic dermatitis and comparison with other north american referral centers. *J Clin Aesthet Dermatol*. 2010; 3:29–35. [PubMed: 20967193]
74. Lever R, Forsyth A. Allergic contact dermatitis in atopic dermatitis. *Acta Derm Venereol Suppl* (Stockh). 1992; 176:95–8. [PubMed: 1476046]
75. Mailhol C, Lauwers-Cances V, Rance F, Paul C, Giordano-Labadie F. Prevalence and risk factors for allergic contact dermatitis to topical treatment in atopic dermatitis: a study in 641 children. *Allergy*. 2009; 64:801–6. [PubMed: 19183418]

76. Fonacier LS, Aquino MR. The role of contact allergy in atopic dermatitis. *Immunol Allergy Clin North Am.* 2010; 30:337–50. [PubMed: 20670817]
77. Giordano-Labadie F, Rance F, Pellegrin F, Bazex J, Dutau G, Schwarze HP. Frequency of contact allergy in children with atopic dermatitis: results of a prospective study of 137 cases. *Contact Dermatitis.* 1999; 40:192–5. [PubMed: 10208505]
78. Kwan JM, Jacob SE. Contact dermatitis in the atopic child. *Pediatr Ann.* 2012; 41:422–3. 6–8. [PubMed: 23052146]
79. Nijhawan RI, Matiz C, Jacob SE. Contact dermatitis: from basics to allergodromes. *Pediatr Ann.* 2009; 38:99–108. [PubMed: 19263785]
80. Zug KA, Rietschel RL, Warshaw EM, Belsito DV, Taylor JS, Maibach HI, et al. The value of patch testing patients with a scattered generalized distribution of dermatitis: retrospective cross-sectional analyses of North American Contact Dermatitis Group data, 2001 to 2004. *J Am Acad Dermatol.* 2008; 59:426–31. [PubMed: 18597890]
81. Nethercott JR, Holness DL. Validity of patch test screening trays in the evaluation of patients with allergic contact dermatitis. *J Am Acad Dermatol.* 1989; 21:568. [PubMed: 2778117]
82. Diepgen TL, Coenraads PJ. Sensitivity, specificity and positive predictive value of patch testing: the more you test, the more you get? ESCD Working Party on Epidemiology. *Contact Dermatitis.* 2000; 42:315–7. [PubMed: 10871093]
83. Jacob SE, Burk CJ, Connelly EA. Patch testing: another steroid-sparing agent to consider in children. *Pediatr Dermatol.* 2008; 25:81–7. [PubMed: 18304161]
84. Moustafa M, Holden CR, Athavale P, Cork MJ, Messenger AG, Gawkrödger DJ. Patch testing is a useful investigation in children with eczema. *Contact Dermatitis.* 2011; 65:208–12. [PubMed: 21504435]
85. Rowlands D, Tofte SJ, Hanifin JM. Does food allergy cause atopic dermatitis? Food challenge testing to dissociate eczematous from immediate reactions. *Dermatol Ther.* 2006; 19:97–103. [PubMed: 16669992]
86. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health technology assessment.* 2000; 4:1–191. [PubMed: 11134919]
87. Bath-Hextall F, Delamere FM, Williams HC. Dietary exclusions for established atopic eczema. *Cochrane Database Syst Rev.* 2008:CD005203. [PubMed: 18254073]
88. Werfel T, Ballmer-Weber B, Eigenmann PA, Niggemann B, Rance F, Turjanmaa K, et al. Eczematous reactions to food in atopic eczema: position paper of the EAACI and GA2LEN. *Allergy.* 2007; 62:723–8. [PubMed: 17573718]
89. Sampson HA. The evaluation and management of food allergy in atopic dermatitis. *Clinics in dermatology.* 2003; 21:183–92. [PubMed: 12781436]
90. Fleischer DM, Bock SA, Spears GC, Wilson CG, Miyazawa NK, Gleason MC, et al. Oral food challenges in children with a diagnosis of food allergy. *J Pediatr.* 2011; 158:578–83 e1. [PubMed: 21030035]
91. Noimark L, Cox HE. Nutritional problems related to food allergy in childhood. *Pediatr Allergy Immunol.* 2008; 19:188–95. [PubMed: 18257908]
92. Hon KL, Nip SY, Cheung KL. A tragic case of atopic eczema: malnutrition and infections despite multivitamins and supplements. *Iran J Allergy Asthma Immunol.* 2012; 11:267–70. [PubMed: 22947914]
93. Penders J, Thijs C, van den Brandt PA, Kummeling I, Snijders B, Stelma F, et al. Gut microbiota composition and development of atopic manifestations in infancy: the KOALA Birth Cohort Study. *Gut.* 2007; 56:661–7. [PubMed: 17047098]
94. Viljanen M, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, et al. Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial. *Allergy.* 2005; 60:494–500. [PubMed: 15727582]
95. Boyle RJ, Bath-Hextall FJ, Leonardi-Bee J, Murrell DF, Tang ML. Probiotics for the treatment of eczema: a systematic review. *Clin Exp Allergy.* 2009; 39:1117–27. [PubMed: 19573037]
96. Hattori K, Yamamoto A, Sasai M, Taniuchi S, Kojima T, Kobayashi Y, et al. Effects of administration of bifidobacteria on fecal microflora and clinical symptoms in infants with atopic dermatitis. *Arerugi.* 2003; 52:20–30. [PubMed: 12598719]

97. Passeron T, Lacour JP, Fontas E, Ortonne JP. Prebiotics and synbiotics: two promising approaches for the treatment of atopic dermatitis in children above 2 years. *Allergy*. 2006; 61:431–7. [PubMed: 16512804]
98. van der Aa LB, Heymans HS, van Aalderen WM, Sillevius Smitt JH, Knol J, Ben Amor K, et al. Effect of a new synbiotic mixture on atopic dermatitis in infants: a randomized-controlled trial. *Clin Exp Allergy*. 2010; 40:795–804. [PubMed: 20184604]
99. Mayser P, Mayer K, Mahloudjian M, Benzing S, Kramer HJ, Schill WB, et al. A double-blind, randomized, placebo-controlled trial of n-3 versus n-6 fatty acid-based lipid infusion in atopic dermatitis. *JPEN J Parenter Enteral Nutr*. 2002; 26:151–8. [PubMed: 12005454]
100. Soyland E, Funk J, Rajka G, Sandberg M, Thune P, Rustad L, et al. Dietary supplementation with very long-chain n-3 fatty acids in patients with atopic dermatitis. A double-blind, multicentre study. *Br J Dermatol*. 1994; 130:757–64. [PubMed: 8011502]
101. van Gool CJ, Zeegers MP, Thijs C. Oral essential fatty acid supplementation in atopic dermatitis—a meta-analysis of placebo-controlled trials. *Br J Dermatol*. 2004; 150:728–40. [PubMed: 15099370]
102. Bamford JT, Gibson RW, Renier CM. Atopic eczema unresponsive to evening primrose oil (linoleic and gamma-linolenic acids). *J Am Acad Dermatol*. 1985; 13:959–65. [PubMed: 3908514]
103. Berth-Jones J, Graham-Brown RA. Placebo-controlled trial of essential fatty acid supplementation in atopic dermatitis. *Lancet*. 1993; 341:1557–60. [PubMed: 8099640]
104. Morse PF, Horrobin DF, Manku MS, Stewart JC, Allen R, Littlewood S, et al. Meta-analysis of placebo-controlled studies of the efficacy of Epogam in the treatment of atopic eczema. Relationship between plasma essential fatty acid changes and clinical response. *Br J Dermatol*. 1989; 121:75–90. [PubMed: 2667620]
105. Senapati S, Banerjee S, Gangopadhyay DN. Evening primrose oil is effective in atopic dermatitis: a randomized placebo-controlled trial. *Indian J Dermatol Venereol Leprol*. 2008; 74:447–52. [PubMed: 19052401]
106. Skogh M. Atopic eczema unresponsive to evening primrose oil (linoleic and gamma-linolenic acids). *J Am Acad Dermatol*. 1986; 15:114–5. [PubMed: 3013957]
107. Henz BM, Jablonska S, van de Kerkhof PC, Stingl G, Blaszczyk M, Vandervalk PG, et al. Double-blind, multicentre analysis of the efficacy of borage oil in patients with atopic eczema. *Br J Dermatol*. 1999; 140:685–8. [PubMed: 10233322]
108. Takwale A, Tan E, Agarwal S, Barclay G, Ahmed I, Hotchkiss K, et al. Efficacy and tolerability of borage oil in adults and children with atopic eczema: randomised, double blind, placebo controlled, parallel group trial. *BMJ*. 2003; 327:1385. [PubMed: 14670885]
109. Bath-Hextall FJ, Jenkinson C, Humphreys R, Williams HC. Dietary supplements for established atopic eczema. *Cochrane Database Syst Rev*. 2012; 2:CD005205. [PubMed: 22336810]
110. Ewing CI, Gibbs AC, Ashcroft C, David TJ. Failure of oral zinc supplementation in atopic eczema. *Eur J Clin Nutr*. 1991; 45:507–10. [PubMed: 1782922]
111. Javanbakht MH, Keshavarz SA, Djalali M, Siassi F, Eshraghian MR, Firooz A, et al. Randomized controlled trial using vitamins E and D supplementation in atopic dermatitis. *J Dermatolog Treat*. 2011; 22:144–50. [PubMed: 20653487]
112. Sidbury R, Sullivan AF, Thadhani RI, Camargo CA Jr. Randomized controlled trial of vitamin D supplementation for winter-related atopic dermatitis in Boston: a pilot study. *Br J Dermatol*. 2008; 159:245–7. [PubMed: 18489598]
113. Tsourelis-Nikita E, Hercogova J, Lotti T, Menchini G. Evaluation of dietary intake of vitamin E in the treatment of atopic dermatitis: a study of the clinical course and evaluation of the immunoglobulin E serum levels. *Int J Dermatol*. 2002; 41:146–50. [PubMed: 12010339]
114. Mabin DC, Hollis S, Lockwood J, David TJ. Pyridoxine in atopic dermatitis. *Br J Dermatol*. 1995; 133:764–7. [PubMed: 8555030]
115. Gutgesell C, Heise S, Seubert S, Seubert A, Domhof S, Brunner E, et al. Double-blind placebo-controlled house dust mite control measures in adult patients with atopic dermatitis. *Br J Dermatol*. 2001; 145:70–4. [PubMed: 11453909]

116. Friedmann PS, Tan BB. Mite elimination--clinical effect on eczema. *Allergy*. 1998; 53:97–100. [PubMed: 10096818]
117. Oosting AJ, de Bruin-Weller MS, Terreehorst I, Tempels-Pavlica Z, Aalberse RC, de Monchy JG, et al. Effect of mattress encasings on atopic dermatitis outcome measures in a double-blind, placebo-controlled study: the Dutch mite avoidance study. *J Allergy Clin Immunol*. 2002; 110:500–6. [PubMed: 12209102]
118. Tsitoura S, Nestoridou K, Botis P, Karmaus W, Botezan C, Bojarskas J, et al. Randomized trial to prevent sensitization to mite allergens in toddlers and preschoolers by allergen reduction and education: one-year results. *Arch Pediatr Adolesc Med*. 2002; 156:1021–7. [PubMed: 12361449]
119. Holm L, Bengtsson A, van Hage-Hamsten M, Ohman S, Scheynius A. Effectiveness of occlusive bedding in the treatment of atopic dermatitis--a placebo-controlled trial of 12 months' duration. *Allergy*. 2001; 56:152–8. [PubMed: 11167376]
120. Andersen PH, Bindslev-Jensen C, Mosbech H, Zachariae H, Andersen KE. Skin symptoms in patients with atopic dermatitis using enzyme-containing detergents. A placebo-controlled study. *Acta Derm Venereol*. 1998; 78:60–2. [PubMed: 9498031]
121. Kiriya T, Sugiura H, Uehara M. Residual washing detergent in cotton clothes: a factor of winter deterioration of dry skin in atopic dermatitis. *J Dermatol*. 2003; 30:708–12. [PubMed: 14684951]
122. Thomas KS, Dean T, O'Leary C, Sach TH, Koller K, Frost A, et al. A randomised controlled trial of ion-exchange water softeners for the treatment of eczema in children. *PLoS medicine*. 2011; 8:e1000395. [PubMed: 21358807]
123. Schmid-Wendtner MH, Korting HC. The pH of the skin surface and its impact on the barrier function. *Skin Pharmacol Physiol*. 2006; 19:296–302. [PubMed: 16864974]
124. Reuter J, Merfort I, Schempp CM. Botanicals in dermatology: an evidence-based review. *Am J Clin Dermatol*. 2010; 11:247–67. [PubMed: 20509719]
125. Robinson MK, Kruszewski FH, Al-Atrash J, Blazka ME, Gingell R, Heitfeld FA, et al. Comparative assessment of the acute skin irritation potential of detergent formulations using a novel human 4-h patch test method. *Food and chemical toxicology: an international journal published for the British Industrial Biological Research Association*. 2005; 43:1703–12. [PubMed: 16026914]
126. Caress SM, Steinemann AC. Prevalence of fragrance sensitivity in the American population. *Journal of environmental health*. 2009; 71:46–50. [PubMed: 19326669]
127. Hermanns JF, Goffin V, Arrese JE, Rodriguez C, Pierard GE. Beneficial effects of softened fabrics on atopic skin. *Dermatology*. 2001; 202:167–70. [PubMed: 11306849]
128. Ricci G, Patrizi A, Bendandi B, Menna G, Varotti E, Masi M. Clinical effectiveness of a silk fabric in the treatment of atopic dermatitis. *Br J Dermatol*. 2004; 150:127–31. [PubMed: 14746626]
129. Senti G, Steinmann LS, Fischer B, Kurmann R, Storni T, Johansen P, et al. Antimicrobial silk clothing in the treatment of atopic dermatitis proves comparable to topical corticosteroid treatment. *Dermatology*. 2006; 213:228–33. [PubMed: 17033173]
130. Vlachou C, Thomas KS, Williams HC. A case report and critical appraisal of the literature on the use of DermaSilk in children with atopic dermatitis. *Clin Exp Dermatol*. 2009; 34:e901–3. [PubMed: 20055862]
131. Gauger A. Silver-coated textiles in the therapy of atopic eczema. *Current problems in dermatology*. 2006; 33:152–64. [PubMed: 16766887]
132. Cadario G, Galluccio AG, Pezza M, Appino A, Milani M, Pecora S, et al. Sublingual immunotherapy efficacy in patients with atopic dermatitis and house dust mites sensitivity: a prospective pilot study. *Curr Med Res Opin*. 2007; 23:2503–6. [PubMed: 17784996]
133. Pajno GB, Caminiti L, Vita D, Barberio G, Salzano G, Lombardo F, et al. Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized, double-blind, placebo-controlled study. *J Allergy Clin Immunol*. 2007; 120:164–70. [PubMed: 17543376]
134. Nahm DH, Lee ES, Park HJ, Kim HA, Choi GS, Jeon SY. Treatment of atopic dermatitis with a combination of allergen-specific immunotherapy and a histamine-immunoglobulin complex. *Int Arch Allergy Immunol*. 2008; 146:235–40. [PubMed: 18268392]

135. Bussmann C, Maintz L, Hart J, Allam JP, Vrtala S, Chen KW, et al. Clinical improvement and immunological changes in atopic dermatitis patients undergoing subcutaneous immunotherapy with a house dust mite allergoid: a pilot study. *Clin Exp Allergy*. 2007; 37:1277–85. [PubMed: 17845407]
136. Werfel T, Breuer K, Rueff F, Przybilla B, Worm M, Grewe M, et al. Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multi-centre, randomized, dose-response study. *Allergy*. 2006; 61:202–5. [PubMed: 16409197]
137. Leroy BP, Lachapelle JM, Somville MM, Jacquemin MG, Saint-Remy JM. Injection of allergen-antibody complexes is an effective treatment of atopic dermatitis. *Dermatologica*. 1991; 182:98–106. [PubMed: 2050242]
138. Leroy BP, Lachapelle JM, Jacquemin M, Saint-Remy JM. Treatment of atopic dermatitis by allergen-antibody complexes: long-term clinical results and evolution of IgE antibodies. *Dermatology*. 1992; 184:271–4. [PubMed: 1498393]
139. Leroy BP, Boden G, Jacquemin MG, Lachapelle JM, Saint-Remy JM. Allergen-antibody complexes in the treatment of atopic dermatitis: preliminary results of a double-blind placebo-controlled study. *Acta Derm Venereol Suppl (Stockh)*. 1992; 176:129–31. [PubMed: 1476025]
140. Glover MT, Atherton DJ. A double-blind controlled trial of hyposensitization to *Dermatophagoides pteronyssinus* in children with atopic eczema. *Clin Exp Allergy*. 1992; 22:440–6. [PubMed: 1611544]
141. Zhang W, Leonard T, Bath-Hextall F, Chambers CA, Lee C, Humphreys R, et al. Chinese herbal medicine for atopic eczema. *Cochrane Database Syst Rev*. 2004;CD002291. [PubMed: 15495031]
142. Hon KL, Chan BC, Leung PC. Chinese herbal medicine research in eczema treatment. *Chin Med*. 2011; 6:17. [PubMed: 21527032]
143. Keane FM, Munn SE, Vivier AW, Higgins EM, Taylor NF. Analysis of Chinese herbal creams prescribed for dermatological conditions. *West J Med*. 1999; 170:257–9. [PubMed: 18751138]
144. Pfaf F, Huss-Marp J, Gatti A, Fuqin J, Athanasiadis GI, Irmich D, et al. Influence of acupuncture on type I hypersensitivity itch and the wheal and flare response in adults with atopic eczema - a blinded, randomized, placebo-controlled, crossover trial. *Allergy*. 2010; 65:903–10. [PubMed: 20002660]
145. Salameh F, Perla D, Solomon M, Gamus D, Barzilai A, Greenberger S, et al. The effectiveness of combined Chinese herbal medicine and acupuncture in the treatment of atopic dermatitis. *J Altern Complement Med*. 2008; 14:1043–8. [PubMed: 18990051]
146. Schachner L, Field T, Hernandez-Reif M, Duarte AM, Krasnegor J. Atopic dermatitis symptoms decreased in children following massage therapy. *Pediatr Dermatol*. 1998; 15:390–5. [PubMed: 9796594]
147. Anderson C, Lis-Balchin M, Kirk-Smith M. Evaluation of massage with essential oils on childhood atopic eczema. *Phytother Res*. 2000; 14:452–6. [PubMed: 10960901]
148. Itamura R. Effect of homeopathic treatment of 60 Japanese patients with chronic skin disease. *Complement Ther Med*. 2007; 15:115–20. [PubMed: 17544862]
149. Lee KC, Keyes A, Hensley JR, Gordon JR, Kwasny MJ, West DP, et al. Effectiveness of acupressure on pruritus and lichenification associated with atopic dermatitis: a pilot trial. *Acupunct Med*. 2012; 30:8–11. [PubMed: 22207450]
150. Pittler MH, Armstrong NC, Cox A, Collier PM, Hart A, Ernst E. Randomized, double-blind, placebo-controlled trial of autologous blood therapy for atopic dermatitis. *Br J Dermatol*. 2003; 148:307–13. [PubMed: 12588384]
151. Niggemann B, Reibel S, Wahn U. The atopy patch test (APT)-- a useful tool for the diagnosis of food allergy in children with atopic dermatitis. *Allergy*. 2000; 55:281–5. [PubMed: 10753020]
152. Sampson HA. Food allergy. Part 2: diagnosis and management. *J Allergy Clin Immunol*. 1999; 103:981–9. [PubMed: 10359874]
153. Niggemann B, Binder C, Dupont C, Hadji S, Arvola T, Isolauri E. Prospective, controlled, multi-center study on the effect of an amino-acid-based formula in infants with cow's milk allergy/intolerance and atopic dermatitis. *Pediatr Allergy Immunol*. 2001; 12:78–82. [PubMed: 11338290]

154. Uenishi T, Sugiura H, Tanaka T, Uehara M. Role of foods in irregular aggravation of skin lesions in children with atopic dermatitis. *J Dermatol.* 2008; 35:407–12. [PubMed: 18705827]
155. Norrman G, Tomicic S, Bottcher MF, Oldaeus G, Stromberg L, Falth-magnusson K. Significant improvement of eczema with skin care and food elimination in small children. *Acta Paediatr.* 2005; 94:1384–8. [PubMed: 16299867]
156. Bath-Hextall F, Delamere FM, Williams HC. Dietary exclusions for improving established atopic eczema in adults and children: systematic review. *Allergy.* 2009; 64:258–64. [PubMed: 19178405]
157. Mabin DC, Sykes AE, David TJ. Controlled trial of a few foods diet in severe atopic dermatitis. *Arch Dis Child.* 1995; 73:202–7. [PubMed: 7492155]

Abbreviations

AAD	American Academy of Dermatology
ACD	allergic contact dermatitis
AD	atopic dermatitis
APT	atopy patch test
DBPCFC	double-blind placebo-controlled oral food challenge
GREAT	Global Resources for Eczema Trials
HDM	house dust mites
IgE	Immunoglobulin E
ICD	irritant contact dermatitis
NIAID	National Institute of Allergy and Infectious Disease
RAST	radioallergosorbant
SCORAD	SCORing Atopic Dermatitis
SORT	Strength of Recommendation Taxonomy
SPT	skin prick test
TCI	topical calcineurin inhibitors
TCM	Traditional Chinese Medicine
TCS	topical corticosteroids
RCT	randomized controlled trial

Publishable Conflict of Interest Statement

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 below information 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. The management of conflict of interest for this guideline complies with the Council of Medical Specialty Societies' *Code of Interactions with Companies*.

Wynnis L. Tom, MD served as an investigator for Anacor receiving no compensation.

James N. Bergman, MD had other relationships with Pediapharm receiving honoraria, and served as a consultant for Pierre-Fabre receiving honoraria.

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

Sarah L. Chamlin, MD, MSCI served on the advisory boards for Anacor, Galderma, Promius, and Valeant receiving honoraria.

David E. Cohen, MD served on the advisory boards and as a consultant for Ferndale Labs, Galderma, and Onset 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.

Steven R. Feldman, MD, PhD, 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. Dr. Feldman recused himself for the drafting of guideline recommendations related to phototherapy.

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

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

Amy S. Paller, MS, MD served as a consultant to Anacor, Galderma, Leo Pharma, Promius, Sanofi/Regeneron, and TopMD receiving honoraria; and was an investigator for Astellas, Galderma, Leo Pharma, and TopMD receiving no compensation.

Eric L. Simpson, MD 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.

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

Lawrence F. Eichenfield, MD served as a consultant for Anacor and Bayer 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 and Astellas receiving no compensation.

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

Disclaimer

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, 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 biological behavior of the disease. This guideline reflects the best available data at the time the guideline was prepared. The results of future studies may require revisions to the recommendations in this guideline to reflect new data.

Table I
Clinical questions used to structure the evidence review for the management and treatment of atopic dermatitis with topical therapies

<ul style="list-style-type: none">• What are the most effective approaches to preventing flares in patients with atopic dermatitis?• What types of educational interventions are used in patients with atopic dermatitis to improve patient outcome, and are they effective?• What is the utility of screening for allergens on the course of atopic dermatitis and what are the suggested testing methods?• What is the effectiveness of dietary interventions such as dietary restriction based on food allergy and sensitization testing, and use of supplements such as evening primrose oil, borage oil, fish oil, pyridoxine, vitamin E, multivitamins, and zinc for the treatment of atopic dermatitis?• What environmental modifications such as house dust mite reduction, choice of clothing, irritant avoidance, and use of detergents can be implemented to influence the course of atopic dermatitis?• What is the effect of allergen-based interventions (e.g., desensitization injections, allergen-antibody complexes of house dust mites) on the course of atopic dermatitis?• What is the effectiveness of complementary therapies such as Chinese herbs and other supplements, homeopathy, and massage therapy for the treatment of atopic dermatitis?

Table II
Recommendation for prevention of flares of atopic dermatitis

Continued use of either topical corticosteroids (1-2× per week) or topical calcineurin inhibitors (2-3× per week) after disease stabilization, to previously involved skin, is recommended to reduce subsequent flares or relapses.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table III
Strength of recommendations for the use of topical therapies for flare prevention and for adjunctive and complementary interventions for treatment of atopic dermatitis

	Strength of Recommendation	Level of Evidence	References
Proactive use of topical corticosteroids	A	I	14, 16-20
Proactive use of topical calcineurin inhibitors	A	I	21-23
Structured education programs	A	I	28-33
Video interventions	B	II	41, 42
Eczema workshops, nurse-led programs	B	II	35-40
Elicit history of environmental and food allergies	B	II	46-48, 151
Allergy assessment if positive history elicited	B	II	46, 51, 52, 56, 65, 71, 151, 152
Patch testing for ACD	B	II	73-75, 83, 84
Against food elimination based on allergy tests only	B	II	87, 153-157
Avoidance if true IgE-mediated allergy	A	I	46, 90
Against routine use of probiotics/Prebiotics for treatment of established AD	B	II	94-98
Insufficient evidence to recommend fish oils, evening primrose oil, borage oil, multivitamin supplements, zinc, vitamin D, vitamin E, and vitamin B12, B6	B	II	99-114
Against routine use of house dust mite covers	B	II	115-119
Against specific laundering techniques or specific products	C	III	120, 121
Insufficient evidence to recommend specialized clothing fabrics	B	II	128-130
Against sublingual and injectional immunotherapy for the general AD population	B	II	132-140
Insufficient evidence to recommend Chinese herbal therapy	C	III	141-143
Insufficient evidence to recommend massage therapy	B	II	146, 147
Insufficient evidence to recommend aromatherapy, naturopathy, hypnotherapy, acupuncture, autologous blood injections	B	II,III	148, 149

Table IV
Recommendations for educational interventions for atopic dermatitis

Educational programs (training programs, “eczema schools”) are recommended as an adjunct to the conventional therapy of AD.
Video interventions can be recommended as an adjunct to conventional therapy.
Eczema workshops and nurse-led programs may be useful as an adjunct to conventional therapy.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table V
Recommendations for testing for co-existing allergic disease

Atopic dermatitis patients have an increased rate of environmental and food allergies and physicians should assess for these conditions during history taking. If significant concerns for allergy are identified (i.e. hives, urticaria, etc.), assessment can be undertaken. Allergy testing independent of history is not recommended.
Patch testing should be considered in AD patients with persistent/recalcitrant disease, and/or a history or physical exam findings consistent with allergic contact dermatitis.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table VI
Recommendations for other adjunctive and complementary interventions for the treatment of atopic dermatitis

Food elimination diets based solely on the findings of food allergy test results are not recommended for the management of AD.
If a patient has a true IgE-mediated allergy, he or she should practice avoidance to prevent potential serious health sequelae.
Children less than 5 years old with moderate to severe AD should be considered for food allergy evaluation for milk, egg, peanut, wheat, and soy if at least one of the following is met: a) persistent AD in spite of optimized treatment or b) having a reliable history of immediate reaction after ingestion of a specific food.
The use of probiotics/prebiotics for the treatment of patients with established AD is not recommended due to inconsistent evidence.
There is inconsistent to no evidence to recommend the use of fish oils, evening primrose oil, borage oil, multivitamin supplements, zinc, vitamin D, vitamin E, vitamin B12 and B6 for the treatment of AD.
There is limited evidence to support the routine use of house dust mite covers to treat patients with AD who are sensitized to dust mites.
The use of specific laundering techniques (such as double rinsing), detergents, or other laundry products cannot be recommended for AD treatment due to the lack of clinical studies.
There is limited evidence to support the use of specialized clothing fabrics in the treatment of AD.
In the general atopic dermatitis population, sublingual immunotherapy and injection immunotherapy are not recommended for the treatment of AD due to a small number of studies and conflicting conclusions.
Chinese herbal therapy and massage therapy have insufficient evidence for recommendation for AD treatment.
The use of aromatherapy, naturopathy, hypnotherapy, acupuncture, or autologous blood injections cannot be recommended for the treatment of atopic dermatitis at this time due to insufficient evidence.