GUIDELINES OF CARE FOR ATOPIC DERMATITIS

Technical Report

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ATOPIC DERMATITIS

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TECHNICAL REPORT – ATOPIC DERMATITIS

Background

A Work Group of dermatologists with recognized expertise in the diagnosis and treatment of atopic dermatatitis was appointed by the president of the American Academy of Dermatology on the recommendation of the Guidelines/Outcomes Task Force in accordance with the administrative regulations from 2000 (see Appendix 1 for a list of experts and reviewers). Representatives from the Guidelines/Outcomes Task Force who had experience in the use of an evidence-based methodology were also appointed to the task force. The Work Group had been assigned topics that corresponded to each clinical question. They received a copy of the vended technical report and attended a live meeting in Chicago in November, 2002 to construct the first rough draft of recommendations and discussion sections. The foundational clinical questions are listed below. The primary audiences for this guideline are practicing dermatologists and dermatology residents but these also may be used for healthcare professionals in cooperation with a licensed dermatologist.

1. Are prevention measures (including exclusion or inclusion) during pregnancy and after birth including dietary and aeroallergens of significant value in preventing the occurrence of atopic dermatitis?

2. In regard to topical corticosteroids, what is the optimal dose, vehicle, frequency of application, and safety, specifically of bones and eyes?

3. What is the effectiveness of the following topicals: coal tar, doxepin, phosphodiesterase inhibitors, emollients, tacrolimus (FK-506/Protopic®), and ascomycin (ASM 981/Elidel®), separately and in combination, for the treatment of atopic dermatitis?

4. What is the effectiveness of antibiotics and antiseptics for the treatment and prevention of atopic dermatitis?

5. How effective are antihistamines in relieving the signs and symptoms of atopic dermatitis?

6. What is the effectiveness of dietary interventions such as dietary restriction in established atopic eczema, evening primrose oil, borage oil, fish oil, pyridoxine, vitamin E and multivitamins, and zinc supplementation for the treatment and prevention of atopic dermatitis?

7. What is the effectiveness of nonpharmacologic approaches such as house dust mite reduction, avoidance of enzyme-enriched detergents, specialized clothing, salt baths, nurse education, bioresonance, psychological approaches and ultraviolet (UV) phototherapy, for the treatment of atopic dermatitis?

8. What is the effectiveness of systemic immunomodulatory agents such as desensitization injections, tumor necrosis factor inhibitors such as Enbrel® (etanercept) and Remicade® (infliximab), allergen-antibody complexes of house dust mites, leukotriene inhibitors, Cyclosporin A, interferon-gamma, thymopentin (TP-5), intravenous immunoglobulin (IVIG), azathioprine, methotrexate, mycophenolate mofetil, prednisone, oral Elidel® (pimecrolimus or ascomycin), theophylline and papaverine for the treatment of atopic dermatitis?

9. What is the effectiveness of complementary therapies such as Chinese herbs, homeopathy, hypnotherapy/biofeedback and massage therapy for the treatment of atopic dermatitis?

These questions were addressed by searching, retrieving, and reviewing the available medical evidence (see **Evaluation of Evidence** that follows) and analyzing materials published in the peer-reviewed medical literature that were relevant to the questions asked.

Evaluation of Evidence

Search strategy: Evidence evaluated for this report was obtained primarily from a search of MEDLINE and EMBASE databases spanning the years 1990 to June 3, 2003. Search terms included *atopic dermatitis* and *atopic eczema* as keywords, subject words, and title words, combined with *treatment, therapy, prevention, and prophylaxis*. Searches were also undertaken for each specific intervention as keyword, subject word, and title word, alone and combined with *atopic dermatitis* and *atopic eczema*. Clinical trials and other sources of information were identified in the results of these searches and in the Clinical Trials Database of the Cochrane Collaboration. Additional trials were identified by handsearching of publications, including reviews, meta-analyses, and correspondence. Only English-language publications were evaluated.

The available evidence was evaluated using methodology described by Goodman (1998) in a document on healthcare technology assessment, prepared for the National Information Center on Health Services Research and Health Care Technology (NICHSR) at the National Library of Medicine.[1] Grading of the level of evidence was done as follows:

- I Properly designed randomized controlled trial.
- II-1 Well-designed controlled trial without randomization.
- II-2 Well-designed cohort or case-control analytic study, preferably from more than one center or research group.
- II-3 Time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence.
- III Clinical experience, descriptive studies, or reports of expert committees.

In addition to these general methodologic considerations, there were some specific issues that were evaluated in each study due to their relevance to the topic of AD. One of these issues is the use of specific criteria for diagnosis of AD and evaluation of disease severity. Standardized, validated criteria for enrolling AD patients and evaluating their disease severity have been described by a number of authors, and are essential to the study of AD and to the comparison of different interventions.[2-7] Another issue of significance for studies of AD is the need for both treatment and time controls. Because AD is characterized by remission and relapse, the natural history of the disease may have a significant impact on symptom manifestations, and may confound interpretation of treatment effects. Study population demographics are also important considerations in evaluation of studies of therapeutic interventions for AD. Although both children and adults are affected by AD, clinical studies do not always include both pediatric and adult patients.

For each intervention within the Clinical Questions, an effort was made to identify and present the best evidence regarding its use in the treatment of AD. Studies of clinical measurements of outcome were considered for analysis whether or not the clinical outcome was the primary outcome measured. The most relevant studies

using patient populations of 20 or more individuals were included in the evidence tables, if more than one such study was available for review and analysis. An overview of the quality and findings of the evidence regarding each intervention is presented before each table, and untabulated studies are described within the text. A brief summary of conclusions is provided at the end of each section for each intervention.

Review Process

In accordance with the revised 2002 administrative regulations, once the final draft is approved by the Guidelines/Outcomes Task Force and the Work Group, this is submitted to the 2nd Expert Review Team. This consisted of 3-5 recognized experts that are given a copy of the draft and have 30 days to comment. This document is then submitted to the Guidelines/Outcomes Task Force and the work group for their approval and if necessary further revision. This process may be repeated as necessary. Once the guideline and technical report is deemed complete by the Guidelines/Outcomes Task Force, it is sent to the members of the Board of Directors for a 30 day comment period. Receipt of Board member comments are acknowledged in writing. Comments are compliled in a standard format to be sent to the work group and task force for comment. The Guidelines/Outcomes Task Force will review the comments and response and act to accept, reject, modify, or request further information. Task Force action on individual Board member comments is conveyed to the Board member via a copy of the formatted comment form.

Concurrent with Board member review, the membership is notified via print and electronic media of the availability of the draft guideline along with the technical report for member review and written comment. The intent of the means of notification is to widely disseminate the notice using standard print and currently available technology, for example, but not limited to *Dermatology World*, e-mail. The guideline will be available as a draft in the Members Only section of the Academy web site for 30 days from the date of the notice. A printed copy of the draft will be available upon request for 30 days from the date of notice. Advance notice of publication is provided to the Advisory Board. Receipt of comments from the membership within the 30 day comment period is acknowledged in writing. Comments are compiled in a standard format and sent to the Guidelines/Outcomes Task Force and work group chairs for response. The Guidelines/Outcomes Task Force will review the comments and response and act to accept, reject, modify, or request further information.

A final draft is approved by the Guidelines/Outcomes Task Force and submitted for approval to the Board of Directors by placement on the Board agenda. Upon approval by the Board of Directors the guideline is posted on the AAD Web site and submitted to the editor of the *Journal of the American Academy of Dermatology* indicating the date of Board approval. The editor is instructed to send galley proofs to the task force through the Academy office and reprint requests to the American Academy of Dermatology.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations

The Academy must ensure balance, independence, objectivity and scientific rigor in its evidence-based guidelines of care. The Board of Directors requires that all participating members of the guidelines of care associated work groups must comply with regulations governing disclosure.

All participants are expected to disclose in the document “Disclosure Form” any significant financial interest or other relationship with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed by them. The intent of this disclosure is not to prevent anyone with a significant financial or other relationship from participating, but rather to provide readers of the guideline with information on which to make their

own judgments. It remains for the reader to determine whether any work member's interests or relationships may influence the discussion. Each of the following Work Group Members have served as a consultant, received research support or clinical research grants from the following companies:

Jon M. Hanifin, MD, Chair Atopic Dermatitis Work Group

3M	Connetics	Ligand
Admirall	Corixa	Novartis
Allergan	Fujisawa	P & G
Berlex	Glaxo Smith Kline	Stiefel
Cellergy	Leo	Taisko

Abby S. Van Voorhees, MD, Chair Guidelines/Outcomes Task Force

Allergan	Genentech
Amgen	Glaxo Smith Kline
Biogen	IDEC
Boehringer/Ingelhein	Merck

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Biogen	Glaxo Smith Kline
Centocor	Fujisawa
Genmab	Proctor & Gamble/Estee Lauder/L'Oreal

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Fujisawa	Novartis
Leo	Allergan
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Sewon Kang, MD
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Bernice R. Krafchik, MD

Fujisawa Canada	Novartis Canada

David J. Margolis, MD
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Lawrence A. Schachner, MD

Ferndell Laboratory	Novartis
Fujisawa	

Robert Sidbury, MD
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Susan E. Whitmore, MD
None

1. **Are prevention measures (including exclusion or inclusion) during pregnancy and after birth including dietary and aeroallergens of significant value in preventing the occurrence of atopic dermatitis?**

Dietary interventions for prevention of atopic dermatitis (AD) have been studied by several authors. Although sample sizes in many studies have been large enough to show significant differences among the results of different feeding strategies, few have reported rigorously defined diagnostic criteria for diagnosing AD, and reported compliance with dietary regimens varies. Specific infant formulas have been compared to one another and to exclusive breast-feeding using groups of infants thought to be at high risk of AD. Several authors[8-12, 17] have reported the results of a number of trials of hypoallergenic formulas and avoidance diets. Results of these trials have been conflicting, with some evidence for successful avoidance of AD in high-risk infants who are exclusively breast-fed for 6 months or longer. Odelram et al. (1996) found no evidence of a protective effect for allergen avoidance, [11] but Bergman et al. (2002) demonstrated an increasing risk of AD with each additional month of breast-feeding.[12] There is also evidence of the benefit of an allergen avoidance diet, including the structured and delayed introduction of sensitivity-provoking foods. However, these benefits may be limited to the first 2 years of life, as Zeiger and Heller, in 1995, reported that at 7 years of age, most differences among feeding groups are gone.[13]

Kalliomaki et al. (2001) and Rautava et al. (2002) examined the effect of dietary supplementation with *Lactobacillus* given prenatally and to nursing mothers of infants.[14,15] These studies suggested that probiotic therapy may be effective in prevention of atopic symptoms in children up to 2 years of age. However, a significant limitation of both of these studies is that the authors did not use rigorous diagnostic criteria in collecting data on the prevalence of AD in their study populations. More studies are necessary regarding probiotic therapy in the perinatal period are needed to further establish the safety efficacy, optimal dosing, duration of treatment as well as the possible effects of various lactobacillus preparations on the development of atopic dermatitis.[14-17]

No studies were available that specifically addressed the avoidance of aeroallergens on the development of AD, and although both Halken et al. (1992), and Marini et al. (1996) included aeroallergen avoidance strategies in their prevention programs,[9,10] others included allergen avoidance instruction as a part of the "regular care" of control patients at high risk for AD.

Summary

The value of preventive dietary measures, including exclusive breast-feeding and exclusion diets has not been shown conclusively to be of value in preventing atopic symptoms in infants at high risk for the development of atopy. There is some conflicting evidence that suggests that it may postpone the emergence of these symptoms until the third year of life or later. Probiotic supplementation has been associated with a protective effect in the first 24 months of life, but rigorous additional studies are needed.

Table 1.–Summary of Studies of Prenatal and Postnatal Atopic Dermatitis Prevention Measures

Key: AD, atopic dermatitis; dx, diagnosis; f/u, follow-up; grp(s), group(s); IgE, immunoglobulin E; NR, not reported; pt(s), patient(s); RCT, randomized controlled trial; SCORAD, SCORing Atopic Dermatitis; tx(s), treatment(s)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Diagnostic Criteria	Results	Comments/Limitations
II-1	**Chandra and Hamed, 1991[8]** Controlled trial to compare the effect of exclusive breast-feeding with 3 different formulas on the development of atopic symptoms in infancy	60 mothers of high-risk infants agreed to exclusive breast-feeding; these infants served as control grp 203 other high-risk infants were given one of the following for 6 mos: Whey hydrolysate formula (n=68) Soy-based formula (n=68) Cows' milk formula (n=67) Infants examined at 12 and 18 mos	Dx of AD based on presence of ≥2 areas of rash, primarily of face, neck, behind ears, and flexural folds	Exclusive breast-feeding or whey hydrolysate formula was associated with similar rates of AD development at 12 and 18 mos. Cows' milk and soy-based formulas resulted in significantly higher rates of AD.	Limitations: No randomization. Breast-feeding mothers had no dietary limitations. All grps were given instruction on gradual introduction of foods thought to cause sensitivities. Compliance with feeding programs NR. Dx of AD not based on validated criteria.
II-2	**Halken et al., 1992[9]** Cohort study to evaluate the effect of an allergy prevention program on the development of atopic symptoms	105 high-risk infants received exclusive breast-feeding or hypoallergenic formula, with families advised on allergen avoidance 54 high-risk infants who received usual care served as a control grp Children examined at 18 mos	Dx of AD based on presence of ≥2 areas of rash, primarily of face, neck, behind ears, and flexural folds	The hypoallergenic diet and withholding of solid food until 6 mos were associated with significant reduction in atopic symptoms at 18 mos AD prevalence at 18 mos: 14% of prevention grp 31% of control grp	Limitations: All mothers in breast-feeding grp were allowed unrestricted diet. Brief f/u period. AD dx not based on validated criteria.

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Diagnostic Criteria	Results	Comments/Limitations
I	**Zeiger and Heller, 1995[13]** RCT to evaluate the effect of food allergen avoidance in infancy on development of atopy in high-risk children	288 mothers of high-risk infants were randomized before the 3rd trimester of pregnancy to receive one of the following: Allergen-avoidance diet – infants were breast-fed and/or supplemented with hypoallergenic formula, with solids introduced in a restricted manner (n=103 at enrollment, 59 evaluated at 7 yrs) Routine prenatal care (n=185 at enrollment, 106 evaluated at 7 yrs) Children followed for 7 yrs	Dx of AD based on presence of recurrent pruritic eruption of typical appearance and a concurrent specific IgE	Prevalence of AD was similar in both grps at 7 yrs. Food allergen avoidance during infancy failed to prevent development of atopy in childhood.	Although only 57% of each grp was available for study at 7 yrs, similar results were seen at earlier intervals Limitations: AD dx not based on validated criteria
II-2	**Marini et al., 1996[10]** Prospective cohort study to evaluate the results of an allergy prevention program over 3 yrs	82 infants at high risk for atopic disease were randomly assigned one of the following: Hydrolyzed milk formula (n=48 at birth, 42 completed the study) Conventional formula (n=47 at birth, 38 completed the study) Parents of these and an exclusively breast-fed grp (n=124 at birth, 104 completed the study) were given environmental and dietary advice. 64 infants who were either breast-fed or received the normal Italian infant diet served as control grp. Children examined at 1, 2, and 3 yrs	Dx of AD based on the presence of scaly erythematous, pruritic rash on ≥2 areas of the face, scalp, behind the ears and in flexural folds. Severity was not assessed.	Data indicate that the allergen-avoidance interventions were effective in reducing the incidence of food and other environmental sensitivities At 3 yrs of age, 37.1% of control grp children and 12.1% of intervention grp children had developed AD	Limitations: Variety of interventions and combinations of diets and interventions reduces size and validity of comparison subgrps. AD dx not based on validated criteria.

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Diagnostic Criteria	Results	Comments/Limitations
I	**Odelram et al., 1996**[11] RCT to investigate whether whey hydrolysate formula, in comparison with routine cows' milk formula could prevent development of atopy in high-risk infants	91 infants at high risk for AD were studied. Infants who were exclusively breast-fed for ≤9 mos were randomized to one of the following at weaning: Hydrolyzed, ultrafiltered cows' milk whey formula (n=32) Standard cows' milk formula (n=39) A control grp of 20 was exclusively breast-fed for >9 mos Children examined at 3, 6, 12, and 18 mos	Dx of atopic disease was based on history and physical exam. Total IgE and cows' milk IgE determined.	No significant protective benefit was seen with the use of whey formula. Immunologic results did not differ between the 2 grps.	Limitations: Exclusive breast-feeding was not continued for a set period. Mothers' and infants' diets varied widely. No specific criteria were reported for AD dx. Severity of disease was not evaluated.
I	**Kalliomaki et al., 2001**[14] RCT to evaluate the effect of administration of probiotics to pregnant/lactating mothers or their infants on the development of atopic disease	159 mothers were randomized to one of the following: Daily oral *Lactobacillus rhamnosus* for 2-4 wks prenatally and 6 mos postnatally (n=77 at enrollment, 64 completed study) Placebo control (n=82 at enrollment, 68 completed study) Children examined during neonatal period and at 3, 6, 12, 18, and 24 mos of age	Development of AD by age 2 was assessed by observation and history of multiple episodes of pruritus and facial and/or extensor involvement, and evaluated for severity using the SCORAD index	Data indicate that administration of probiotics may have a preventive effect on the development of AD. 23% of infants in the experimental grp developed AD, compared with 46% in the control grp. The avg disease severity was similar in affected infants from both grps.	Limitations: Mothers who did not breast-feed exclusively fed the medication to their infants, though similar results were seen in either type of administration. AD dx not based on validated criteria.
II-2	**Bergman et al., 2002**[12] Observational birth cohort study to determine the effect of breast-feeding on the development of AD	1314 of 7609 infants born in 6 hospitals during 1990 were recruited for study of feeding practices and development of symptoms. 499 were at high risk for development of AD. Children examined at 1, 3, 6, 12, 18, and 24 mos of age, and annually thereafter	Development of AD assessed by exam using validated criteria, with questionnaires and structured interviews used to provide data on intervening periods	Risk of AD increased with each additional mo of breast-feeding	Limitations: Nonexclusive breast-feeding was considered part of the breast-feeding interval 71% of participants completed the study, with families with known atopic disease having a significantly higher participation rate

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Diagnostic Criteria	Results	Comments/Limitations
I	**Rautava et al., 2002**[15] RCT to evaluate the effect of administration of probiotics to pregnant/lactating mothers on the development of atopic disease	62 mothers were enrolled and randomized to one of the following for 4 wks prior to delivery and during 3 mos of breast-feeding: Daily oral *Lactobacillus rhamnosus* (n=30) Placebo (n=32) 57 mother/infant pairs completed the study Children examined at 3, 6, 12, 18, and 24 mos of age	Development of AD in 1st 24 mos of life assessed by clinical exam and history of ≥3 episodes of pruritus with typical morphology and distribution. Serum IgE and specific antibody to cows' milk were determined.	Administration of probiotics may have a preventive effect on the development of AD 15% of infants whose mothers received probiotics were diagnosed with AD. 47% of infants whose mothers received placebo developed AD. No immunologic markers investigated differed significantly between the 2 grps	Limitations: Small sample size, very loosely defined criteria for dx All pts are described as coming from atopic families, with 16 mothers in the probiotics grp and 22 in the placebo grp diagnosed with atopic disease Authors note that 55% of the 22 pts born to atopic mothers in the placebo grp were found to have AD by age 2 yrs

2. In regard to topical corticosteroids, what is the optimal dose, vehicle, frequency of application, and safety, specifically of bones and eyes?

Topical corticosteroids, first introduced in the early 1950s, have been the mainstay of therapy for atopic dermatitis (AD) for many years.[21,35] This class of drugs is generally the standard to which other therapies are compared. Dermatologists and other medical specialists have employed topical corticosteroids with apparently acceptable safety and effectiveness based on consistent widespread prescribing and patient acceptance of these medications. Recommended dosing regimens have been established by the drug manufacturers, based on the results of phase III clinical trials leading to drug approval. However, there is relatively little evidence regarding optimal treatment protocols for specific conditions, such as AD, or for specific patient populations, such as pediatric patients. Additionally, although the question of prophylactic corticosteroid therapy has been raised, there is no evidence to support any type of prophylactic therapy for AD other than nonprescription emollients and general skin care.[18-20] In a comprehensive review of therapies for AD, Hoare et al. (2000) noted that randomized controlled trials using different regimens for topical corticosteroids therapy must be performed to provide guidance for the best use of these medications.[21]

In addition to the lack of evidence regarding optimal dosing regimens for corticosteroids, there is also little published evidence regarding potential noncutaneous side effects of topical corticosteroid therapy. As a precaution, it is recommended that patients receiving topical corticosteroid therapy for chronic conditions be evaluated for risk factors for suboptimal linear growth and reduced bone density, and that these patients be instructed to ingest adequate calcium and Vitamin D.[22-23,46-47,57-58,60-65] Questions regarding the relationship between topical application of corticosteroids to the eyelids and subsequent development of cataracts and/or glaucoma have been raised, however currently there is insufficient evidence to adequately address these concerns.[22-25]

Available evidence regarding optimal dose, frequency, vehicle, and safety issues of topical corticosteroid therapy for patients with AD has been summarized in the following sections, along with a table describing available topical corticosteroid preparations.

Optimal dose

There is little evidence regarding the optimal dose of corticosteroids for treatment of AD. The best evidence for establishing the optimal dose of a particular drug is found by studying the efficacy of a range of doses in large numbers of patients. Studies in the peer-reviewed medical literature of the efficacy of individual formulations of specific corticosteroids[26-29] do not provide evidence of dose optimization. Rather, they document the efficacy of particular preparations. Clinical trials that compare the efficacy of one drug to that of another[18,30-34] typically compare the effect of a new drug with an established preparation, without establishing optimal dosage for either.

Three studies that evaluated different dosages of corticosteroids were identified in the peer-reviewed literature; these studies provided no definitive evidence that differences in drug potency are associated with differences in efficacy. Two of these studies addressed therapeutic options such as inpatient admission and wet-wrap dressings, and therefore the findings may not be applicable to patient self-care or different types of dressings. Ainley-Walker et al. (1998) retrospectively reviewed the

hospital charts of 82 inpatient admissions in which patients with AD received differing treatments on either side of the body. Evaluation of disease extent and severity was performed by clinicians blinded to treatment. Topical corticosteroids of varying potency were compared in 31 of these left-right comparison subjects. The less potent corticosteroid was more effective in 5 cases; there was no difference in 10 cases; and the moderately potent corticosteroid was more effective in 16 comparisons.[35] Wolkerstorfer et al. (2000) investigated the efficacy of three different dilutions of corticosteroid used in wet-wrap dressings for 18 children with severe AD. After 1 week of treatment, there was no apparent difference in the clinical effect of the different concentrations.[37]

Vehicle

Very little evidence has been published in the peer-reviewed medical literature on the relative safety or efficacy of the vehicles used in the formulation of topical corticosteroid medications. In a study of 150 adult patients, Cato et al. (2001) reported that the clinical response to treatment of target AD lesions with topical corticosteroid therapy was improved by the absorption-enhancing chemical laurocapram.[39] However, validated diagnostic and severity scoring criteria were not reported by the authors. Yuninger and Calobrisi (2001) investigated the reactions of 14 known peanut-sensitive adults and children to a refined peanut oil used in the formulation of topical medications and found no immediate or delayed skin reactivity.[41] These results were confirmed by Paller (2003).[40]

Frequency of application

Several studies were identified in the peer-reviewed medical literature that investigated the optimal frequency of application of topical corticosteroids in the treatment of AD, with no conclusive results. Aalto-Kote and Turpeinen (1995) measured absorption of hydrocortisone in adult patients with widespread AD.[42] Their results suggested that the absorption of topical hydrocortisone is more rapid in damaged skin than after healing has begun. They inferred that twice-daily dosage is advantageous for the first 24 hours, and once-daily dosage is appropriate thereafter, however, this assumption remains to be proven. Bleehen et al. (1995) and Tharp (1996) compared the effects of daily and twice-daily treatment with topical fluticasone propionate cream .05% in a 4-week study of 270 adult and pediatric AD patients. No differences in clinical outcomes were demonstrated between the two frequencies of application.[43,44] Two other investigations, one utilizing adult patients[19] and one involving both adults and children,[45] evaluated the effectiveness of twice-weekly application of fluticasone propionate cream for preventing relapse in populations of patients who had achieved remission of symptoms with daily therapy. Both studies reported that the twice-weekly application was more effective than placebo therapy in preventing relapse of AD. However, these studies failed to establish that the twice-weekly treatment protocol was more effective than other treatment schedules. Thomas et al. (2002) compared the effect of short bursts of 0.1% betamethasone valerate to 1% hydrocortisone cream administered continuously. No differences in clinical outcomes were noted.[38]

These studies addressing frequency of topical corticosteroid application have been summarized in the following table.

Table 2a.–Summary of Studies of the Frequency of Application of Topical Corticosteroids in the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; dx, diagnosis; f/u, follow-up; grp(s), group(s); HPA, hypothalamic-pituitary-adrenal; pt(s), patient(s); RCT, randomized controlled trial; SCORAD, SCORing Atopic Dermatitis; tx(s), treatment(s)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/Limitations
I	**Bleehen et al., 1995**[43] RCT to compare the efficacy and safety of once-daily with twice-daily application of fluticasone propionate in the tx of AD symptoms	270 adult and pediatric pts with moderate-to-severe AD were randomized to receive one of the following for 4 wks: 0.05% fluticasone propionate cream twice daily (n=137) 0.05% fluticasone propionate cream once daily and placebo cream once daily (n=133) 197 pts completed the study Pts evaluated at baseline and after 4 wks of tx	Clinical response of a preselected target area was assessed by blinded investigators; categorized as cleared, excellent, or good	No significant clinical differences were seen between the 2 study populations Few adverse effects noted, including local burning and exacerbation of AD	*Limitations*: No diagnostic criteria noted. Assessment criteria not clearly described. Evaluation of target lesion, rather than overall severity, used for assessment. Brief study period. 27% dropout rate.
I	**Tharp, 1996**[44] RCT to compare the efficacy and safety of once-daily with twice-daily application of fluticasone propionate in the tx of AD symptoms	238 pts 12+ yrs of age with moderate-to-severe AD were randomized to receive one of the following for 28 days: 0.05% fluticasone propionate cream once daily and placebo cream once daily (n=79) 0.05% fluticasone propionate cream twice daily (n=79) 0.05% placebo cream once daily (n=80) 183 pts completed the study Pts were evaluated at baseline and wkly after tx was started	The same investigator rated all pts on 6-point scale for improvement and severity. A 7-point scale was used for rating of target lesion.	No statistical difference seen between 2 fluticasone tx grps at end of study. Both grps improved compared with placebo grp. Few adverse effects noted, none systemic	Large study population. Vehicle-only control grp utilized. *Limitations:* Diagnostic criteria not described. Evaluation of target lesion, rather than overall severity, used for assessment. 23% dropout rate.

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/Limitations
I	**Van Der Meer et al., 1999[19]** RCT to evaluate the effect of intermittent therapy with topical fluticasone propionate in the tx of AD symptoms	54 adult pts with moderate-to-severe AD who were considered completely healed after 4 wks of daily tx with fluticasone propionate were randomized to receive one of the following once daily, 2 days/wk for 16 wks: 0.05% fluticasone propionate cream (n=23) Placebo cream (n=31) 32 pts completed the study Pts were evaluated at entry into the randomized study and 4, 8, and 16 wks after twice-wkly tx was started	Extent and severity of AD evaluated using SCORAD index. Target lesions were graded on a 0-3 scale for severity.	A significant increase in AD symptoms was reported for the placebo grp compared to the tx grp 68% of placebo grp and 39% of tx grp left study during 16-wk study period due to exacerbations of AD symptoms	Validated dx and severity scoring criteria used, along with a target lesion scoring system described by the authors. The open phase of the study included 112 pts, of whom 56 were considered completely healed after the initial 4 wks of more frequent tx. *Limitations:* High dropout rate due to exacerbation of AD symptoms, especially in placebo grp
I	**Hanifin et al., 2002[45]** RCT to evaluate the effect of intermittent therapy with topical fluticasone propionate in the tx of AD symptoms	348 adult and pediatric pts with moderate or severe AD who achieved tx success after up to 4 wks of twice-daily tx with fluticasone propionate were randomized to receive one of the following once daily, 2 days/wk for 16 wks: 0.05% fluticasone propionate cream (n=229) Placebo cream (n=119) 32 pts completed the study Pts were evaluated at entry into the randomized study and 4, 8, and 16 wks after twice-weekly tx was started	Efficacy measured by investigator using 6-point global assessment scale and body surface area measurements	Tx grp was 7.7 times less likely to relapse than pts in control grp Median time to relapse calculated as 4.7 wks for control grp. This could not be calculated for tx grp, as most pts remained in remission after 16 wks of twice-wkly tx. 2 subjects in 44-wk safety phase exhibited potential HPA axis suppression. No cases of skin atrophy were reported.	Validated dx and severity scoring criteria used. Both grps received daily emollient tx. *Limitations:* 91% dropout rate

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/Limitations
I	**Thomas et al., 2002[38]** RCT to compare the effect of intermittent topical therapy with a potent corticosteroid with continuous therapy with a mild topical corticosteroid in the tx of mild-moderate AD.	174 pediatric pts (age range 1-15 yrs) with mild or moderate AD were randomized to receive 1 of the following topical txs for a week with AD flares for eighteen weeks. 0.1% betamethasone valerate ointment for 3 days followed by vehicle control for 4 days 1% hydrocortisone ointment for 7 days Pts were evaluated at baseline and every 6 weeks during tx. 165 pts completed the study.	Total number of scratch-free days and relapses recorded by pts on 5 point scale. Relapses defined as 3 days of scoring 2 or greater.	Median number of scratch-free days: Continuous tx grp; 118.0 Intermittent grp; 117.5 Relapses were the same in both grps. No adverse effects were noted.	Both tx regimens produced significant clinical improvement compared to baseline assessment Validated dx and severity scoring criteria used. *Limitations:* Tx was given in 7-day bursts as required during the 18-week study period.
I	**Paller et al., 2003[40]** RCT to evaluate the effect of topical fluocinolone acetate 0.01% in a peanut oil vehicle in the tx of AD	94 pts (age range 2-12 yrs) with AD affecting at least 20% of body surface area were randomized to receive one of the following topical txs twice daily for 2 weeks: Fluocinolone acetate 0.01% in a peanut oil vehicle Peanut oil vehicle control The active medication was then given to all pts for 2 weeks, and peanut oil vehicle was dispensed for the final 2 weeks. Pts were evaluated at baseline and every 2 weeks during the study period.	Assessment of severity made by clinicians on 4 point scale at 4-8 target areas Effect of the active medication on the HPA axis assessed by laboratory analysis.	A good response (>50% clearance) was observed in 54.3% of pts in active tx grp, and 12.2% of control grp. No HPA axis suppression seen. No serious adverse effects were noted.	*Comments:* Fluocinolone acetate 0.01% in a peanut oil vehicle tx was associated with significant clinical efficacy. Pts with known peanut allergy were included in this study, with no adverse reactions to refined peanut oil vehicle.

Safety, specifically of bones and eyes

Questions regarding potential adverse effects of topical corticosteroid therapy, such as bone loss, have arisen due to the hypothalamic-pituitary-adrenal (HPA) axis suppression that has been associated with chronic corticosteroid therapy for other diseases[46, 47] and the association of steroid use and cataracts.[48] Few investigations have been undertaken to study the specific effect of topical corticosteroid use on HPA axis function or the corneas of patients being treated for AD. However, corticosteroid use is carefully monitored, particularly in pediatric patients, who may have greater systemic absorption of active medication. There have also been local adverse effects, such as burning and pain at the applications sites, reported with topical corticosteroid therapy for AD.

The potential for topical corticosteroid therapy to suppress the HPA axis in pediatric patients has been investigated in a small number of studies, with no conclusive results. Rasmussen (1978) did not observe HPA axis suppression in 7 children with AD studied,[49] although HPA axis suppression has been reported in children and percutaneous absorption documented in adults by other investigators.[50,51] Lucky et al. (1997) reported no effect on the HPA axis in 20 pediatric patients with AD treated with either topical desonide or hydrocortisone.[52] Although increased absorption of topical corticosteroid has been documented in patients with more severe disease and those less than 2 years of age, Matsuda et al. (2000) found evidence to suggest that factors other than dosage and disease severity may cause HPA axis suppression in patients with AD.[53] In a study of 18 patients receiving therapy with wet-wrap dressings, Wolkerstorfer et al. (2000) observed HPA axis suppression in 8 children receiving the highest of three concentrations of fluticasone propionate, with no differences in clinical outcomes among the three treatment groups.[34] Friedlander et al. (2002) noted HPA axis suppression in 2 of 43 very young children with moderate-to-severe AD treated with fluticasone for 4 weeks.[55]

There is very little evidence regarding the potential association of topical corticosteroid with increased risk of cataracts or glaucoma. Tan et al. (2001) reported the results of an *in vitro* study of eyelid skin excised during cosmetic blepharoplasty.[54] Only very small amounts of fluticasone ointment were detected as having penetrated this skin when examined up to 48 hours after application, suggesting that the degree of ocular absorption is minor. However, clinical trial data are lacking regarding ocular effects of topical steroid therapy.

Evidence from the reviewed clinical trials is summarized in the following table.

Table 2b.–Summary of Studies of the Effect of Topical Corticosteroids on the HPA Axis in Patients with Atopic Dermatitis

Key: ACTH, adrenocorticotropic hormone; AD, atopic dermatitis; f/u, follow-up; grp(s), group(s); HPA, hypothalamic-pituitary-adrenal; pt(s), patient(s); RCT, randomized controlled trial; SCORAD, SCORing Atopic Dermatitis; tx(s), treatment(s)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/Limitations
I	**Lucky et al., 1997[52]** Randomized trial to compare the effects of 0.05% desonide and 2.5% hydrocortisone ointments on the HPA axis function of pts with AD	20 pediatric pts with AD affecting at least 20% of body surface randomized to receive one of the following twice daily for 28 days: 0.05% desonide ointment (n=10) 2.5% hydrocortisone ointment (n=10) 15 pts completed the study Early morning cortisol levels determined before tx and on days 14 and 28. ACTH-stimulated mean cortisol values determined before tx and on day 28.	HPA axis suppression assessed by laboratory evaluation of early morning cortisol levels and by the determination of ACTH-stimulated mean cortisol values	No significant differences were seen in either early morning cortisol levels or ACTH-stimulated mean cortisol values	No HPA axis suppression was noted for either of the medications studied *Limitations:* Small study population w/ 25% dropout rate. No diagnostic criteria noted. Relatively brief study period. No clinical results of tx reported.
II-3	**Friedlander et al., 2002[55]** Open-label safety study to evaluate the effects of 0.05% fluticasone propionate cream on the HPA axis function of pts with AD	51 pediatric pts received tx with 0.05% fluticasone propionate cream twice daily for 3 to 4 wks 43 pts completed the study Pts evaluated wkly	HPA axis suppression assessed by laboratory pre- and post-stimulation cortisol levels	Mean stimulated and unstimulated cortisol levels were similar before and after tx. 2 children exhibited HPA axis suppression.	Other steroid use was not allowed within 1 wk of study entry or during study *Limitations:* No diagnostic criteria noted. Broad variation in severity of disease in tx grp leading to wide variation in the amount of medication used.

Summary

Optimal dose
Very little evidence is available in the peer-reviewed medical literature to determine the optimal dose of the many topical steroid formulations available, and the available evidence is conflicting. Efficacy of prescribing regimens and dosages has been established, but with little clinical investigation of optimization. There is no medical evidence to support topical corticosteroid use that differs from manufacturers' guidelines or to support topical corticosteroid use as prophylactic therapy.

Vehicle
The peer-reviewed medical evidence provides little information on the optimal vehicle for delivering medication in the treatment of AD.

Frequency of application
There is insufficient evidence to determine optimal frequency of corticosteroid application, however there are some data to suggest that once-daily treatment is as effective as twice-daily applications. There is also some data that suggests that pulse therapy with more potent corticosteroids is as effective as chronic therapy with less potent agents.

Safety, specifically of bones and eyes
There is a very limited amount of evidence to suggest that topical corticosteroid therapy has the potential to affect HPA function. However, it is unclear whether this adverse effect is associated with a particular corticosteroid preparation, dosing schedule, or patient population. Further investigation of the manner in which topical corticosteroid use affects linear growth in children and bone density of children and adults is needed. Little information is available regarding an association between topical corticosteroid use and cataracts or glaucoma.

3. What is the effectiveness of the following topicals: coal tar, doxepin, phosphodiesterase inhibitors, emollients, tacrolimus (FK-506/Protopic®), and ascomycin (ASM 981/Elidel®), separately and in combination, for the treatment of atopic dermatitis?

The efficacy and safety of some of these interventions have been addressed by the peer-reviewed literature, but some are not supported by more than a few clinical trials. Most studies did not describe the use of rigorous, validated diagnostic criteria or severity scoring, such as the criteria of Hanifin and Rajka[2] or the SCORAD (SCORing Atopic Dermatitis) index.[4] No studies of these drugs administered in combination were identified in the literature search.

Coal tar
Although crude coal tar and preparations including coal tar derivatives have been used for many years in the treatment of skin diseases, the significant cosmetic disadvantages of coal tar preparations are likely to make it unacceptable to patients and influence compliance. There have been few scientifically valid trials of coal tar preparations that focus on the clinical efficacy in treatment of AD. Munkvad (1989) investigated therapy with a specially prepared coal tar preparation designed to be more cosmetically acceptable to patients than traditional preparations. In a left-/right-paired comparison study lasting 4 weeks, Munkvad found that this new coal tar preparation was as effective as 1% hydrocortisone cream, and similarly

acceptable to patients. Five of 30 patients in this study complained of itching and soreness related to the coal tar cream, with 1 patient reporting this as an effect of the hydrocortisone preparation.[66]

Doxepin

Two large, randomized trials of doxepin cream for treatment of AD were identified in the peer-reviewed literature. Doxepin cream has been used in the treatment of AD because of its antihistaminic, antipruritic effects. In a randomized, double-blind study in 1994, Drake et al. found that significantly more patients treated with 5% doxepin cream experienced relief of pruritus related to AD than patients given a vehicle-only control cream. Drowsiness was another side effect noted by many patients, but it was found to be transient in nature.[67] Berberian et al. (1999) compared the effect of 4 therapies: hydrocortisone alone, triamcinalone acetonide alone, hydrocortisone and doxepin in combination, and triamcinalone acetonide and doxepin in combination. In this study, the addition of doxepin resulted in a significantly more rapid relief of itching improvement in underlying AD.[68]

Evidence from the reviewed studies is summarized in the following table.

Table 3a.–Summary of Studies of Topical Doxepin in the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; f/u, follow-up; grp(s), group(s); pt(s), patient(s); RCT, randomized controlled trial; tx(s), treatment(s) or therapy(ies)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/Limitations
I	**Drake et al., 1994[67]** RCT to evaluate the safety and efficacy of doxepin cream in relieving pruritus associated with AD	270 pts (mean age 33 yrs) with AD who had moderate-to-severe pruritus for at least 1 wk were randomized to tx with one of the following for 7 days: Vehicle cream placebo (n=138) 5% doxepin cream (n=132) Pts were evaluated on days 1, 3, and 7	AD and pruritus evaluated by physician on 3-point scale. Daily pruritus score self-reported by pt on 100-point visual analog scale.	Significantly higher proportion (85%) of doxepin-txd pts reported relief of pruritus compared with control grp (57%) Localized burning or stinging reported by 39 pts in doxepin grp, 34 pts in control grp	60% of pts reported relief of pruritus within 24 hrs of beginning doxepin tx. Other medications were withdrawn before study period. *Limitations:* Short study period
I	**Berberian et al., 1999[68]** RCT to compare the effect of topical corticosteroid plus doxepin with topical corticosteroid alone on pruritus associated with AD	349 pts with AD who had moderate-to-severe pruritus for at least 1 wk were randomized to receive one of the following topical txs for 8 days: 2.5% hydrocortisone (n=83) 0.1% triamcinalone acetonide (n=90) 2.5% hydrocortisone and 5% doxepin (n=86) 0.1% triamcinalone acetonide and 5% doxepin (n=90) Pts were evaluated 12 hrs after initiation of tx and on days 2, 3, 4, and 8	AD and pruritus evaluated by physician on 3-point scale. Daily pruritus score self-reported by pt on 100-point visual analog scale.	The addition of doxepin to the tx regimen resulted in more rapid reduction in pruritus scores Transient drowsiness noted by 38% of pts receiving hydrocortisone and doxepin and 10% of pts receiving triamcinalone acetonide and doxepin compared to 9 % and 5% for the respective steroids alone	Other medications were withdrawn before study period *Limitations:* Short study period

Phosphodiesterase inhibitors
A trial of topical application of the phosphodiesterase inhibitor CP80,633, conducted by Hanifin et al. (1996) demonstrated significant clinical improvement in 20 adult patients beginning on day 3 of treatment and continuing through day 28.[69] Griffiths et al. (2002) demonstrated effectiveness superior to vehicle of the type 4 phosphodiesterase inhibitor cipamfylline cream but it was less than hydrocortisone 17-butyrate cream in a 2 week trial.[93]

Emollients
Few investigators have studied the effects of emollients alone on the severity of AD symptoms. Three clinical trials were reviewed. One retrospective left/right comparison study of hospitalized patients (Ainley-Walker et al., 1998) reported that 7 of 21 patients demonstrated similar improvement with emollient therapy only, and that for 2 patients, emollient therapy was superior to topical corticosteroid.[35] In a controlled trial, Hanifin et al. (1998) demonstrated that use of an emollient cream can enhance therapeutic response in children and adults.[70] Finally, results of a preliminary trial of a ceramide-dominant lipid moisturizer suggested that this type of emollient may be more effective than currently available moisturizer formulations.[71]

Evidence from the reviewed studies is summarized in the following table.

Table 3b.–Summary of Studies of Emollients in the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; f/u, follow-up; grp(s), group(s); pt(s), patient(s); RCT, randomized controlled trial; SCORAD, SCORing Atopic Dermatitis; tx(s), treatment(s) or therapy(ies)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
I	**Hanifin et al., 1998[70]** RCT to evaluate the effects of adding a moisturizing regimen to a low-potency topical corticosteroid lotion for tx of AD	80 pediatric and adult pts with mild-to-moderate AD on both sides of the body received twice-daily applications of 0.05% desonide lotion to one side of the body and twice-daily applications of 0.05% desonide lotion plus thrice-daily applications of a moisturizing cream on the opposite side for 3 wks. 72 pts completed the study. Pts were assessed at baseline and after tx period	Efficacy was assessed by scoring 7 symptoms from 0-9, with overall global assessment of improvement made by blinded investigator	Combined regimen was associated with significantly greater reduction in severity of AD	*Limitations:* 5 daily applications of lotion/cream may not be easily comparable to most tx regimens
III	**Chamlin et al., 2001[71]** Uncontrolled prospective trial of ceramide-dominant barrier-repair moisturizer in the tx of AD	21 pediatric pts with moderate-to-severe AD who were already receiving optimal topical tx substituted the study moisturizer for their usual emollient and applied it twice daily for 6 wks Pts were evaluated after 3 and 6 wks of tx	Efficacy was assessed using SCORAD measurements	Almost all subjects demonstrated reduction in severity of AD, with most severely affected pts receiving greatest benefit	*Limitations:* Brief study period, small sample size, uncontrolled

Tacrolimus (FK-506/Protopic®)

A large number of studies were identified that addressed the efficacy and safety of topical therapy with tacrolimus for AD. Both adult and pediatric study populations were included in these studies, and many of the studies utilized validated diagnostic and scoring criteria, such as the eczema area and severity index (EASI) score.[72] Dropout rates in some of these studies were high, but were generally highest in control groups who experienced little or no improvement.

One of these studies, a 3-week placebo-controlled study involving pediatric and adult patients, demonstrated that tacrolimus therapy had a beneficial effect on AD symptoms, although no dose-related response was demonstrated.[73] Significant numbers of patients complained of transient burning at the site of application; however this was rarely a reason for withdrawal from the study. Another group[74] confirmed this observation in a longer trial with pediatric patients, and also saw little differences among the dosages they provided. Paller et al. (2001) reported very similar results.[75]

Reitamo et al. (2000) and Sugiura et al. (2000) reported that long-term use of tacrolimus ointment was safe and generally well tolerated by patients.[76,77] This was confirmed by Soter et al. (2001), who reported on the safety of this drug as used by a large group of patients for up to 12 weeks.[78] The clinical efficacy of tacrolimus in two concentrations was studied in these patients and reported to be superior to vehicle alone, with a significant additional reduction in overall severity for the group receiving a higher concentration of active medication.[79] This group used tacrolimus ointment on the face and neck, with few adverse effects. Another group reported few and transient side effects in a group of 255 children treated twice daily with 0.1% tacrolimus ointment for up to 1 year.[80]

Reitamo et al. compared two concentrations of tacrolimus ointment to a midpotency corticosteroid in two large, multicenter, randomized controlled trials, describing slightly different results in pediatric and adult patient populations.[81,82] In children, both concentrations of tacrolimus ointment appeared more effective than corticosteroid, with the higher concentration associated with the greatest reduction in severity.[81] In adults, similar improvement was noted in the corticosteroid and 0.1% tacrolimus ointment groups, and lesser benefit in a group using 0.03% tacrolimus ointment.[82]

Tacrolimus is available in 2 strengths; 0.1% and 0.03%. The stronger formulation is not approved for use in patients younger than 16 years. The weaker formulation is approved for patients age 2 and older.[82-83] Tacrolimus topical therapy is not approved for patients under 2 years of age.[81]

Evidence from the reviewed studies is summarized in the following table.

Table 3c.–Summary of Studies of Topical Tacrolimus in the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; dx, diagnosis; EASI, eczema area and severity index; f/u, follow-up; grp(s), group(s); pt(s), patient(s); RCT, randomized controlled trial; tx(s), treatment(s)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/Limitations
I	**Ruzicka et al., 1997[73]** RCT to compare the effect of three concentrations of tacrolimus ointment to each other and to vehicle alone in the tx of AD	213 pediatric and adult pts were randomized to receive one of the following txs twice daily to 200-1000 cm^2 affected skin for 3 wks: 0.03% tacrolimus ointment (n=54) 0.1% tacrolimus ointment (n=54) 0.3% tacrolimus ointment (n=51) Vehicle-only placebo (n=54) The affected area was assessed at baseline and after tx	The tx area was graded by a blinded physician for symptom severity and a self-reported pruritus score was provided by the pt	Tx with each of the three concentrations of tacrolimus was more effective than tx with vehicle-only placebo. Higher doses were not associated with significantly greater benefit.	Only emollient tx was allowed during study period. Validated diagnostic criteria used for enrollment of pts. *Limitations:* Relatively brief study period. Dose-related transient burning noted at application sites in all 3 tacrolimus grps. Small tx site used. Dropout rate in control grp: 39%
I	**Boguniewicz et al., 1998[74]** RCT to determine the safety and efficacy of tacrolimus ointment in the tx of moderate AD	180 pediatric pts with AD were randomized to receive one of the following txs twice daily for 12 wks: 0.03% tacrolimus ointment (n=43) 0.1% tacrolimus ointment (n=49) 0.3% tacrolimus ointment (n=44) Vehicle-only placebo (n=44) 169 pts completed the study Pts were evaluated at baseline and after 4, 8, and 22 days of tx	Blinded investigators evaluated extent and severity of AD using EASI index scoring. Overall assessment included pts' self-reported pruritus score.	A significantly higher percentage of pts in the tx grps had a "marked-to-excellent" improvement in AD symptoms. No statistically significant differences were found among the three tx grps.	All other tx was withdrawn during the study period. Very low dropout rate (10%).

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/Limitations
I	**Hanifin et al., 2001[79]** RCT to evaluate the safety and efficacy of tacrolimus ointment in the tx of adult pts with AD	In two separate identical trials, 632 adult pts with moderate-to-severe AD were randomized to receive tx to all affected areas twice daily with one of the following for up to 12 wks: 0.03% tacrolimus ointment (n=211) 0.1% tacrolimus ointment (n=209) Vehicle-only placebo (n=212) 374 pts completed the study Pts were evaluated at baseline and after 1, 2, 3, 6, 9, and 12 wks of tx	Clinical evaluations were based on the physician's global evaluation at end of tx	More pts receiving tacrolimus demonstrated significant improvement compared w/ vehicle control. The higher concentration was associated with greater reduction in severity of AD symptoms than the lower concentration. No serious adverse effects were noted	Validated dx and severity scoring criteria used along with an overall scoring system described by the authors *Limitations:* Very high (68.4%) dropout rate in control grp. Adverse event rate 12.3% in higher concentration tacrolimus grp.
I	**Paller et al., 2001[75]** RCT to determine the safety and efficacy of tacrolimus ointment in the tx of moderate AD	351 pediatric pts with AD were randomized to receive one of the following txs twice daily for 12 wks: 0.03% tacrolimus ointment (n=117) 0.1% tacrolimus ointment (n=118) Vehicle-only placebo (n=116) 169 pts completed the study Pts were evaluated at baseline and after 1, 2, 3, 6, 9, and 12 wks of tx	Primary measure of efficacy was global assessment rated by blinded investigators assessing target evaluation areas on 7-point scale from "cleared" to "worse." EASI index was also used for scoring severity and extent of disease.	Tacrolimus ointment appeared to be more effective than vehicle control in all efficacy parameters measured. No statistical difference was seen between the 2 tx grps. No adverse event occurred at a statistically higher rate in the tx grps than in the control grp	Other tx was not allowed during study and washout periods *Limitations:* High dropout rate (56%) in control grp
I	**Reitamo et al., 2002[81]** RCT to compare the effect of topical tx with 2 concentrations of tacrolimus ointment to tx with a mid-potency corticosteroid ointment on symptoms of AD in children	560 pts (age 2-15 yrs) with moderate-to-severe AD were randomized to receive one of the following topical txs for 3 wks: Tacrolimus ointment 0.03% (n=185) Tacrolimus ointment 0.1% (n=189) Hydrocortisone-17-butyrate ointment 0.1% (n=186) 506 pts completed study period Pts were evaluated at baseline, days 3 and 7, and wks 2, 3, and 5	Severity of AD symptoms scored using EASI index plus self-reported assessment of itching by pts	Both grps receiving tacrolimus showed significantly greater benefit than the corticosteroid grp, with the higher tacrolimus concentration grp having the greatest reduction of symptoms 19.9% of pts in 0.1% tacrolimus grp experienced transient skin burning with application of ointment	Validated dx, scoring criteria. Other tx was not allowed during study and washout periods. *Limitations:* Relatively brief tx period.

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/Limitations
I	**Reitamo et al., 2002[82]** RCT to compare the effect of topical tx with 2 concentrations of tacrolimus ointment to tx with a mid-potency corticosteroid ointment on symptoms of AD in adults	570 pts (age ≥16 yrs) with moderate-to-severe AD were randomized to receive one of the following topical txs for 3 wks: Tacrolimus ointment 0.03% (n=186) Tacrolimus ointment 0.1% (n=193) Hydrocortisone-17-butyrate ointment 0.1% (n=191) 509 pts completed study period Pts were evaluated at baseline, days 3 and 7, and wks 2, 3, and 5	Severity of AD symptoms scored using EASI index plus self-reported assessment of itching by pts	There was no significant difference in response between the higher potency tacrolimus grp and the mid-potency corticosteroid grp, with lower concentration tacrolimus associated with significantly less benefit. 59.2% of pts receiving higher concentration of tacrolimus reported transient adverse local effects	Validated dx, scoring criteria. Other tx was not allowed during study and washout periods. Similar (9%-11%) dropout rates for all grps. *Limitations:* Relatively brief study period

Ascomycin (ASM 981/Elidel®/pimecrolimus)

Several reports of randomized clinical trials of ascomycin were available for analysis. The first, a relatively small trial using adult patients by Van Leent et al. (1998) reported few adverse events and low systemic accumulation of the drug following topical use.[84] Harper et al. (2001), in an open study of topical ascomycin therapy for young children, also reported low systemic absorption.[85] Results of a dose-ranging study by Luger et al. (2001) comparing three concentrations of ascomycin cream to both vehicle control and midpotency corticosteroid cream suggested that 0.05% ascomycin cream may not be effective, and that 1% ascomycin cream, while effective, is associated with burning at the application sites for some patients, and has less efficacy than midpotency topical corticosteroid therapy.[86] Eichenfield et al. (2002) studied 1% ascomycin in a vehicle-controlled trial of 6 weeks of topical therapy in children with AD, and observed a pronounced reduction in pruritus and other symptoms, with no systemic accumulation of the drug.[87] Ho et al. (2003)[89] similarly demonstrated efficacy of 1% ascomycin cream in infants in a vehicle controlled trial over a 6 week period. Three studies, Wahn et al. (2002)[92,] Meurer et al. (2002)[91,] and Kapp et al.(2002)[90] showed that 1% ascomycin cream could be ulilized to prevent flares of AD in children, adults and infants respectively.[89-92]

Elidel® cream is approved for use by patients who are 2 years of age or older (FDA, 2002).[88]

Evidence from the reviewed studies is summarized in the following table.

Table 3d.–Summary of Studies of Topical Ascomycin in the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; dx, diagnosis; EASI, eczema area and severity index; f/u, follow-up; grp(s), group(s); pt(s), patient(s); RCT, randomized controlled trial; tx(s), treatment(s)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
I	**Van Leent et al., 1998**[84] RCT to evaluate the safety and effectiveness of ascomycin ointment in the tx of AD, and compare the effect of once- to twice-daily application of the ointment	38 adult pts with moderate-to-severe AD treated one identified test area with tacrolimus ointment and another with vehicle-only placebo cream for 21 days Pts were randomized to one of the following grps: Once-daily application (n=20) Twice-daily application (n=18) 27 pts completed the study Pts were evaluated at baseline and on days 4, 11, and 21	Clearance or partial clearance was evaluated by blinded investigators using a modified symptom index scoring tool	All 3 grps showed improvement over the course of the trial, but the tx grps demonstrated significantly greater reduction in AD severity, and the grp receiving tx twice daily was the most improved Few adverse effects were noted, and little systemic accumulation of the drug was found	Dx and scoring of severity performed using modification of validated scoring tool. Use of 1% hydrocortisone was allowed on nontest areas. Pts were not allowed to use emollient on test sites. *Limitations:* Small sample size, confounding use of other medications

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
I	**Luger et al., 2001[86]** RCT to evaluate the safety and efficacy of 4 concentrations of ascomycin cream in the tx of AD	260 adult pts with moderate-to-severe AD were randomized to tx of all affected areas of the skin for up to 3 wks with one of the following: 0.05% ascomycin ointment (n=42) 0.2% ascomycin ointment (n=46) 0.6% ascomycin ointment (n=42) 1.0% ascomycin ointment (n=45) Midpotency corticosteroid cream (n=42) Vehicle-only placebo (n=43) 199 pts completed the study	Extent and severity of AD assessed using EASI index scoring system. Overall assessment of AD was self-reported by pts at the end of the study.	Use of ascomycin cream in 3 highest concentrations was associated with significant improvement of AD symptoms. The corticosteroid cream was more effective than the highest concentration of ascomycin investigated. Very few adverse effects reported. Transient burning at application sites was the most common adverse effect.	Validated criteria used for dx and scoring of extent, severity of AD *Limitations:* 61 (23%) pts dropped out, more in the control and lowest-potency ascomycin grps

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
I	**Eichenfield et al., 2002[87]** RCT to evaluate the safety and efficacy of ascomycin topical tx	403 pediatric pts with moderate-to-severe AD were randomized to receive tx twice daily to affected areas with one of the following for 6 wks: 1% ascomycin cream (n=267) Vehicle-only placebo (n=136) 339 pts completed the study Pts were evaluated at baseline and on days 8, 15, 22, 29, and 43	Assessment of global severity made by blinded investigators using 6-point scoring system. EASI scoring used to score extent and severity of AD symptoms. Pruritus was reported by the primary caregiver.	Significantly more pts were free of AD symptoms after 6 wks tx than control grp pts. Significantly more pts in tx grp than control grp reported mild or no pruritus. Occurrence of adverse events was similar in tx and control grps, and included transient burning at application sites. No evidence of systemic accumulation found.	Validated diagnostic criteria and severity scoring described. Other txs withdrawn during study, except for additive-free bland emollient. *Limitations:* 25% of vehicle-only grp discontinued the study, compared to 11.2% of tx grp pts
I	**Ho et al., 2003[89]** RCT evaluate the safety & efficacy of topical ascomycin cream in the tx of AD	186 infants (age range 3 - 23 mos with mild-to-moderate moderate AD were randomized to receive tx twice daily to affected areas with one of the following for 6 wks: Ascomycin cream 1% Vehicle control Pts were evaluated at baseline and on days 8, 15, 22, 29, and 43.	Assessment of severity by blinded investigators using EASI scoring system. Pruritus was reported by caregiver assessment.	Assessment as "clear" or "almost clear" Ascomycin grp: 54% Control grp: 23.8% Most adverse reaction were mild similar in tx and control groups.	*Comments:* Validated diagnostic criteria and severity scoring describe. *Limitations:* Reports of caregivers highly subjective. Relatively brief study period.

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
I	**Kapp et. al 2002[90]** RCT to evaluate the safety and efficacy of topical ascomycin in the tx of AD flares.	251 infants (age range 3-23 months) were randomized 4:1 to receive one of the following topical txs twice daily for early AD signs and symptoms for 1 yr: Ascomycin cream 1% (n=204) Vehicle control (n=47)	Assessment of severity made by blinded investigators using Investigators' Global Assessment scale 6 point scale.	Ascomycin cream significantly reduced the incidence of AD flares. 67.6% of tx grp reported flares. 30.4% of control grp reported flares within 6 months.	Validated diagnostic criteria and severity scoring described *Limitations:* Varying duration of tx for flares. High dropout rate.
I	**Meurer et al., 2002[91]** RCT to evaluate effect of ascomycin cream in the long-term management of AD	192 adult pts with moderate to severe AD were randomized to receive one of the following topical txs twice daily for early AD signs and symptoms for 24 weeks Ascomycin cream 1% (n=96) Vehicle control n=(96)	Efficacy was assessed by comparing the number of days rescue medication was used.	Mean days of steroid use: Ascomycin grp; 14.2% Control grp; 37.2% Significant improvement reported in quality of life.	*Comments:* Validated diagnostic criteria and severity scoring described *Limitations:* Varying duration of tx for flares. High dropout rate. Prednicarbate cream was used as rescue medication by both gps.
I	**Wahn et.al, 2002[92]** RCT to determine the efficacy and safety of ascomycin cream in the long-term management of AD	713 pts (mean age 8 yrs, range 2-17) were randomized 2:1 to receive one of the following topical txs for early AD signs and symptoms for 1 yr. Ascomycin cream 1% Vehicle control	Efficacy was assessed by monitoring the need for topical corticosteroid tx.	Incidence of flares was twice as high in control grp compared to tx grp.	Validated diagnostic criteria and severity scoring described *Limitations:* All pts used moderately potent topical corticosteroids for tx of flares.

Summary

Evidence from the peer-reviewed literature suggests that coal tar and coal tar derivatives can reduce the severity of AD symptoms, but barriers to compliance persist.

There is evidence that use of topical doxepin as short-term adjunctive therapy is safe, and may reduce the severity of pruritus associated with AD.

Although it has been suggested that topical therapy with phosphodiesterase inhibitors may be valuable in controlling the symptoms of AD, there has been little clinical research to support this.

There is some evidence, although relatively weak that emollients used in combination with other topical therapies may aid in reducing the severity of AD symptoms.

There is evidence that tacrolimus (FK-506/Protopic®) can be effective in reducing the severity of AD symptoms in both children and adults, with few side effects reported after up to 1 year of treatment. The data are insufficient to define an optimal concentration for use in children or adults.

There is evidence that therapy with ascomycin (ASM 981/Elidel®/ pimecrolimus) is safe and effective for reducing the severity of symptoms in children and adults with mild and moderate AD for up to one year of treatment.

4. What is the effectiveness of antibiotics and antiseptics in the treatment and prevention of atopic dermatitis?

Several studies were identified that evaluated the effects of antibiotics and antiseptics in the treatment of atopic dermatitis (AD). Research involving clinically infected subjects was not selected for analysis, but several studies of the effect on management of bacterial colonization were identified. All used participant groups of 50 or fewer, including adult and pediatric subjects.

Nearly all adults and children with AD are colonized with *Staphylococcus aureus* in their affected and unaffected skin,[94] and antibiotics are generally used to control clinically infected exacerbations of the condition. Two reports are summarized that describe the use of oral antibiotics in the treatment or prevention of AD symptoms. Ewing et al. (1998) monitored compliance closely and documented eradication of colonizing organisms, but demonstrated no clinical improvement associated with antibiotic use.[94] Boguniewicz et al. (2001) demonstrated similar results.[98] In addition to the reports reviewed in the following table, Kolmer et al. (1996) reported that 5 patients with severe AD who were refractory to conventional treatment responded to antifungal therapy. In 4 of these patients, fungal colonization of the skin could be demonstrated by skin cultures.[99]

Three studies of antiseptics or topical antibacterial agents revealed no evidence to indicate their efficacy in children or adults. Stalder et al. (1992) reported no difference between treatment of 20 children with two different antibacterials, and attributed the improvement in both groups to continued use of topical corticosteroids.[100] Ainley-Walker et al. (1998) saw no differences in left-to-right comparisons of hospitalized children treated for AD with seven different topical antibacterials on one half of their bodies.[35] Breneman et al. (2000) reported significant improvement compared to baseline in both treated and placebo groups, although the treated patients had significantly better mean overall severity scores than the placebo patients.[101]

Combination topical antibiotic (eg. fusidic acid) and topical steroid products have shown efficacy in one study,[103], when in others they were no more effective than topical steroid alone.[21] Lever et al. (1988)[102] found clinical improvement followed eradication of skin pathogens, but also found that when post-treatment bacterial counts returned to pre-treatment levels, the clinical improvement persisted. Ramsay et al. (1996)[103] documented that the clinical effect of a combination topical therapy containing fusidic acid 2% and hydrocortisone acetate 1% was more effective in the tx of AD than either ingredient alone.

Summary

Although the reduction of bacterial colonization in the affected and unaffected skin of AD patients by oral and topical antibiotic and antiseptic agents has been demonstrated, there is little evidence of specific efficacy for the reduction of the severity of dermatitis. All of the reviewed studies reported that the antibiotic and antiseptic agents used in the treatment of AD were well tolerated by both pediatric and adult patients.

Evidence from the reviewed studies is summarized in the following tables.

Table 4a.–Summary of Studies of Oral Antibiotics for the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; f/u, follow-up; grp(s), group(s); NR, not reported; pt(s), patient(s); RCT, randomized controlled trial; tx(s), treatment(s)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
I	**Ewing et al., 1998[94]** RCT to evaluate the effect of tx with an oral antibiotic on pts with AD who did not have clinical signs of bacterial infection	50 children with AD were randomized to one of the following for 4 wks: Oral flucloxacillin (n=25) Placebo (n=25) 37 pts completed the entire study Pts examined after 2, 4, 6, and 12 wks	Extent and severity of AD scored using a scoring system devised by the authors. Pts and evaluators recorded overall efficacy scores. Skin cultures were performed to quantify bacterial colonization	No significant differences in clinical measurements were seen between grps Bacterial colonization was reduced, but reappeared within 2 wks of tx cessation No adverse effects noted	Reduction of bacterial colonization in affected and unaffected areas does not lead to reduction of severity of AD Limitations: Blinding of evaluators NR
II-1	**Boguniewicz et al., 2001[98]** Crossover trial to evaluate the clinical effect of tx with an oral antibiotic on pts with AD who did not have clinical signs of bacterial infection	20 pts with AD were randomized to receive oral cefuroxime axetil or placebo for 2 wks, and crossed over to the other grp after a 1-wk washout period All pts continued to use medium-potency steroid cream	Clinical severity was monitored in all pts. Skin cultures were performed to quantify bacterial colonization at the end of each tx period.	No clinical differences seen between grps. Significant reduction in bacterial colonization seen during tx. Bacterial eradication seen in 9 pts, but pts were quickly recolonized No adverse effects noted	Reduction of bacterial colonization in affected and unaffected areas does not lead to reduction of severity of AD Limitations: Severity scoring methods NR, blinding of evaluators NR

Table 4b –Summary of Studies of Topical Antibiotics for the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; f/u, follow-up; grp(s), group(s); NR, not reported; pt(s), patient(s); RCT, randomized controlled trial; tx(s), treatment(s)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
I	**Lever, et al. 1988**[102] RCT to evaluate the effect of topical mupirocin on skin bacterial colonization and in the tx of AD.	49 pts (2 yrs old and older) who did not require systemic antibiotics were enrolled in a crossover trial to receive topical tx with mupirocin ointment or vehicle control for 2 weeks before crossing to other study grp for 2 weeks. Pts were evaluated at baseline and after 2, 4, 6, and 8 weeks.	Bacterial colonization was determined by laboratory analysis of organisms cultured directly from skin. Pts were assessed by blinded clinicians on 0-3 scale at 16 body sites.	Bacterial counts decreased significantly during tx with active preparation. Return to pre-tx levels occurred within 4 weeks following cessation of tx. Significant clinical improvement noted during tx period	*Comments:* Recolonization was not associated with clinical deterioration. Grading system described, unvalidated. *Limitations:* All pts received tx with topical corticosteroid throughout the study period.

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
I	**Ramsay et al., 1996[103]** RCT to evaluate the effect of topical fusidic acid in the tx of AD.	Study I 174 pts (age 3 yrs and older) with mild-to moderate AD were randomized to receive on of the following topical txs for 2 weeks: Fusidic acid 2% and hydrocortisone acetate 1% cream (n=91) Hydrocortisone acetate 1% cream (n=83) 154 pts completed the study. Study II 65 pts (age 3 yrs and older) with mild-to moderate AD were randomized to receive on of the following topical txs for 2 weeks: Fusidic acid 2% and hydrocortisone acetate 1% cream (n=33) Fusidic acid 2% cream (n=32)	Severity was assessed by blinded clinicians on a 4 point scale. Overall severity was assessed by clinicians and pts. Data from pts with known pathogens was analyzed separately from total grps. Tx failure was defined as less than 50% reduction in severity or withdrawal from study. Successful bacteriological response defined as eradication of pre-tx pathogens.	Study I: No significant differences were seen between total gps. Pts with demonstrable pathogens at baseline showed significant improvement over baseline. Study II: Fusidic acid 2% and hydrocortisone acetate 1% cream demonstrated significantly greater efficacy than fusidic acid 2% cream. No significant differences were seen between pts with demonstrable pathogens at baseline and total grps. Both txs were effective at eradicating pathogens	*Comments:* Pooled results indicated the greatest clinical response to fusidic acid 2% and hydrocortisone acetate 1% cream, less response to hydrocortisone acetate 1% cream, and least response to fusidic acid 2% cream. *Limitations:* No placebo control grp. Relatively brief study period.

Table 4c.–Summary of Studies of Topical Antiseptics for the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; f/u, follow-up; grp(s), group(s); $KMnO_4$, potassium permanganate; pt(s), patient(s); RCT, randomized controlled trial; tx(s), treatment(s)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/Limitations
II-2	**Stalder et al., 1992[100]** RCT to compare the bacteriological effects with clinical effects of 2 topical antiseptics	20 children with AD were randomized to one of the following for 1 wk: Chlorhexidine (n=10) $KMnO_4$ (1:20,000) (n=10) Pts continued to use topical steroid tx	Extent and severity of AD was assessed using clinical scoring tool not provided	No differences were noted between the effects of the 2 antibacterials. Both antibacterial agents were well tolerated, and both grps improved similarly.	*Limitations:* Method of tx is not described. No control grp was provided for comparison; brief tx period. Blinding NR. Authors attributed similar, modest improvements in both grps to steroid tx.
II-1	**Ainley-Walker et al., 1998[35]** Retrospective chart review to compare the effect of topical corticosteroid alone with corticosteroid combined with antibacterial agent on AD severity	42 children hospitalized for tx of AD received tx with topical corticosteroid on one side of the body and corticosteroid combined with an antibacterial agent on the other side	Extent and severity of AD assessed by blinded evaluators, who were instructed to make left/right comparisons	23 pts demonstrated no difference between the 2 txs Antibacterial with corticosteroid appeared more effective in 11 cases, while corticosteroid was judged to be more effective in 8 cases	*Limitations:* 7 different antibacterials were used; very small No. of pts in each subset tx grp. Validated rating system used for study entry, but subsequent evaluation made using modified burn charts, and not reported quantitatively. Length of tx varied widely.
I	**Breneman et al., 2000[101]** RCT to determine the effect of antibacterial soap on AD severity and bacterial colonization	50 pts with moderately severe AD were randomized to one of the following for 6 wks: Daily bath with antimicrobial soap containing 1.5% triclocarban (n=25) Daily bath with nonmedicated placebo soap (n=25) After tx period, both grps used placebo for 3-wk washout period Topical steroid cream was provided to all pts	Severity of AD measured using validated criteria and global assessment by blinded evaluator. Bacterial colonization quantified with skin cultures. Use of steroid cream was estimated by weighing used containers.	Antibacterial soap was associated with reduction in severity of AD and reduction of bacterial colonization Pediatric and adult pts included; no adverse effects reported. Overall scores for both grps improved during tx period and worsened during posttx regression period. Similar amounts of topical steroid used by both grps.	*Limitations:* Validated rating system used for entry into study, but only the global assessment score was reported

5. How effective are antihistamines in relieving the signs and symptoms of atopic dermatitis?

Several studies evaluating the use of antihistamines in the treatment of atopic dermatitis (AD) were identified and evaluated. Most of these were published before 1995, and although most were randomized controlled trials, only one studied a population of 50 or more individuals. After review of the available literature, only studies with population sizes over 20 were selected for analysis.

An evidence-based review of the relevant literature[104] found no large randomized, double-blind clinical trials of antihistamines for AD published between 1966 and 1999. This analysis of the literature provided no evidence to support the effectiveness of nonsedating antihistamines. Safety studies, such as the large group reported on by the Early Treatment of the Atopic Child (ETAC) Group[105] suggest that antihistamines are safe, and are not associated with significant adverse effects, even in very young patients.

Only one large, double-blind, placebo-controlled trial of antihistamine therapy for AD was available for review.[106] This was a dose-ranging study that reported a dose-related effect of cetirizine on pruritus but little effect on other symptoms. Wahlgren et al. (1990) found no difference between pruritus scores in patients treated with sedating and nonsedating antihistamines, and further, that the effects noted were not different from the results seen in his placebo-treated patients.[107] Monroe reported in 1992 that hydroxyzine is associated with significantly more sedative side effects than loratadine when used to treat AD for 1 week, but the relief of symptoms seen in the treatment group did not differ significantly from that reported by placebo-treated control patients.[108] In a small study, La Rosa et al. (1994) noted rapid reduction in pruritus in AD patients treated with cetirizine compared with patients receiving placebo, but this effect did not persist.[109]

A brief report by Doherty et al. (1989) of a study of 44 patients suggested that two nonsedating antihistamines, terfenadine and acrivastine, can partially relieve pruritus in AD, but their results did not generally reach statistical significance.[110] In a smaller study of 16 patients, Langeland et al. (1994) described 9 as responsive to antihistamine treatment, with little effect noted in 7 others.[111]

Summary

There is little evidence that sedating or nonsedating antihistamines are effective in the treatment of AD. For sedating antihistamines, it can be difficult to distinguish antipruritic or other clinical effects from the sedative effect; reported improvements in disease severity and quality of life may be due primarily to promotion of restful sleep rather than a reduction in symptoms.

Evidence from the reviewed studies is summarized in the following table.

Table 5.–Summary of Studies of Antihistamines in the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; f/u, follow-up; grp(s), group(s); pt(s), patient(s); RCT, randomized controlled trial; tx(s), treatment(s) or therapy(ies)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/Limitations
I	**Wahlgren et al., 1990**[107] Double-blind, randomized, crossover study to evaluate efficacy of a sedative and a nonsedative antihistamine for tx of AD	25 adult pts with AD were randomized to one of the following txs 2x/day for 3 days, and crossed over to each of the other grps after a 4-day washout period: Terfenadine (60 mg) Clemastine (2 mg) Placebo Use of topical hydrocortisone was allowed during washout periods and monitored Evaluation of pruritus was made after each tx period	Pruritus was self-evaluated on a visual analog scale at the end of each tx period and tracked hrly using a computerized portable data logger	Similar results were observed for all 3 txs. The intensity of pruritus and the use of topical medications did not differ among grps. Clemastine was significantly more sedating than terfenadine.	Neither sedating nor nonsedating antihistamine reduced pruritus. *Limitations:* Brief study period. Limited, self-reported data collection.
I	**Monroe, 1992**[108] RCT to study the relative safety and efficacy of loratadine and hydroxyzine for tx of AD	41 adult pts were randomized to one of the following for 1 wk: Loratadine, 10 mg/day (n= 14) Hydroxyzine, 50 mg/day (n=14) Placebo (n=13) Any topical txs in place at the time of entry into the study were continued. Pts were evaluated after 1 wk.	Pruritus was evaluated by self-reported diary scores. A global evaluation was made by a physician at the end of the study.	Daily pruritus scores decreased for all 3 grps. Sedation was reported by significantly more pts receiving hydroxyzine than the other 2 grps.	Although some pts on study medication reported relief of pruritus, this did not reach statistical significance when compared with the placebo grp *Limitations:* Diagnostic criteria for entry into study not described. Brief study period.

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/Limitations
I	**Hannuksela et al., 1993[106]** RCT to determine the effect of cetirizine in tx of AD	176 adult pts with moderate-to-severe AD were randomized to one of the following for 8 wks: Cetirizine, 10 mg/day (n=42) Cetirizine, 20 mg/day (n=45) Cetirizine, 40 mg/day (n=47) Placebo (n=42) Pts were evaluated after 2 and 4 wks	Intensity of pruritus was self-reported by visual analog scale; skin condition evaluated by blinded physician using 14-area, 4-point scale for erythema, vesicles, excoriation, and lichenification	Higher doses of cetirizine were associated with partial relief of pruritus, but have little effect on skin lesions Sedation was reported by 10/45 pts receiving 20 mg cetirizine/day and 19/47 pts receiving 40 mg cetirizine/day	Similar amounts of topical medications and emollients were used by all grps *Limitations:* Blinding of evaluators not described
I	**La Rosa et al., 1994[109]** RCT to evaluate clinical efficacy of antihistamine tx for pruritus in AD	22 pediatric pts with AD dx were randomized to one of the following for 8 wks: Cetirizine (n=11) Placebo (n=11) Pts were evaluated after 4 and 8 wks	Intensity of pruritus and erythema self-reported. Cutaneous manifestations recorded by blinded clinicians using a clinical severity scale using 20 areas of the body scored for 7 manifestations of AD.	Cetirizine appeared to have an early effect on pruritus, but this did not persist after 8 wks of tx. There was little effect on other symptoms of AD.	Rigorous criteria used in dx. No side effects were noted. *Limitations:* Use of topical medications not described

6. What is the effectiveness of dietary interventions such as dietary restriction in established atopic eczema, and evening primrose oil, borage oil, fish oil, pyridoxine, vitamin E and multivitamins, and zinc supplementation for the treatment and prevention of atopic dermatitis?

Dietary restriction

Several randomized controlled trials and descriptive studies evaluating the effect of dietary restriction on AD were identified in the literature search. Study size ranged from 50 to 100 patients, and most of the studies involved infants or young children. Some investigators reported very high dropout rates, which they attributed to the difficulties presented by a highly restrictive diet to patients and their parents. Few studies used validated diagnostic criteria, and although most authors described their scoring systems, these systems were often unique to the individual study, which hampers comparison of findings.

Sloper et al. (1991) found that 64 patients with AD who completed several weeks on an egg- and cows' milk-free diet experienced improvement in AD symptoms.[112] Subsequently, however, only cows' milk challenge tests were associated with exacerbation of AD. The benefit of an egg-free diet is unclear; in this study, patients who improved on the restricted diet did not respond to a subsequent food challenge with eggs, while a randomized controlled trial by Lever et al. (1998) found that an egg-free diet was associated with an improvement in severity of AD.[113] Mabin et al. (1995) found that a very restrictive diet did not have a significant effect on the severity of AD in young children, and the very high dropout rate in this study suggests that such a diet is very difficult to maintain.[114] A separate study of this highly restricted diet found it to be nutritionally inadequate.[115] A descriptive study (Isolauri et al., 1999) involving exclusively breast-fed infants evaluated the effect of restricting their mothers' diet and eliminating highly allergenic foods on the severity of AD and growth and nutrition of these infants. This study found that for some infants for whom this was not effective, cessation of breast-feeding was associated with improvement in AD.[116] In another descriptive study, Worm et al. (2000) identified subpopulations of responders and nonresponders to restriction of various food additives, however only some of these responding patients reacted to food challenges after the study period ended, making it difficult to identify the specific food additives that might be involved in the AD disease process for each individual.[117]

Evidence from the reviewed studies is summarized in the following table.

Table 6a.–Summary of Studies of Dietary Restriction in the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; dx, diagnosis; f/u, follow-up; grp(s), group(s); NR, not reported; pt(s), patient(s); RCT, randomized controlled trial; tx(s), treatment(s)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/Limitations
II-3	**Sloper et al., 1991[112]** Prospective trial to evaluate the effect of food challenges on the extent and severity of AD in pts who had improved on a food elimination diet.	91 children (mean age 4.5 yrs) with AD were given usual care until improvement ceased; then begun on a diet avoiding cows' milk, eggs, and foods to which they were known to be intolerant. 78 pts completed the study Pts were evaluated at the beginning and end of the diet period, and after food challenges 64 children showed improvement and were offered random order, double-blind food challenges	Extent and severity of AD assessed using chart dividing body into 20 areas and determining the presence or absence of 4 symptoms in each area	64 pts experienced improvement in AD symptoms. Only cows' milk challenge tests were associated with exacerbation of AD.	Study periods varied, adjunctive txs varied, dietary elements varied among pts. 48% of food challenges were incomplete. *Limitations:* Dx, extent, and severity of AD assessed using nonvalidated criteria. Seasonal variations in disease may have affected results, as 47% entered the study in spring.
I	**Mabin et al. 1995[114]** RCT to evaluate the effect of a few foods diet on extent and severity of AD	85 children (mean age 2.3 yrs) with AD were randomized to one of the following diets for 6 wks: A diet of 5 to 8 foods supplemented with whey hydrolysate formula (n=27) A diet of 5 to 8 foods supplemented with whey casein formula (n=32) Usual diet (n=26) Pts were evaluated after 6 wks	An arbitrary scoring method was used to assess extent of skin involvement. Parents reported symptoms using a questionnaire.	Both tx and control grps showed improvement during study period. The restricted diets showed no significant tx effect on severity or extent of AD.	Dx of AD was made using validated criteria *Limitations:* Severity and extent of disease were assessed using arbitrary and subjective measures. Some pts in all grps used antihistamines. 39 (46%) pts dropped out of study due to inability to follow diet
I	**Lever et al., 1998[113]** RCT to evaluate the effect of egg-exclusion diet on severity of AD	55 young children with AD and known sensitivity to eggs were randomized to one of the following for 4 wks: Advice on egg-exclusion diet (n=28) General advice only (n=27)	Extent of AD measured by using "rule of nines". Severity measured using arbitrary scoring method.	Significant reduction in extent and severity of AD was seen in the egg-exclusion grp	*Limitations:* Diagnostic criteria NR, brief tx period, various topical tx continued

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/Limitations
III	**Isolauri et al., 1999[116]** Descriptive study to evaluate the effect of exclusive breast-feeding severity of AD	100 infants with AD were studied during exclusive breast-feeding Infants were evaluated after cessation of breast-feeding. Growth was assessed at 6, 9, and 12 mos.	Extent and severity of AD measured using validated criteria, pt growth and nutrition assessed by measuring body length	Growth slowed with onset of AD, and although some improvement was seen with restricted diet for mothers, weaning to hypoallergenic formulas resulted in overall improvement	Prolongation of breast-feeding with limitations on maternal diet was attempted prior to discontinuing breast-feeding *Limitations:* 55% of infants received donor breast milk in the hospital nursery. Mother and infant diets varied widely. Topical tx NR.
III	**Worm et al., 2000[117]** Descriptive study to evaluate the effect of food additives on severity AD	50 pts with AD were monitored for 4 wks of regular diet followed by 6 wks of a diet low in fruit, sugar, and food additives such as stabilizers and preservatives. Pts who improved on the diet received oral challenges with suspected provocative agents. 41 pts completed the study Pts were evaluated every 2 wks	Severity of AD measured using validated criteria and quantitative scoring by a single evaluator	63% of pts who completed the study showed significant improvement while on the additive-free diet. The other pts showed little or no improvement. Only a subgrp of pts with improvement of symptoms reacted to blinded food challenges.	*Limitations:* Unblinded study, brief study period. Topical tx NR.

Evening primrose oil, fish oil, and borage oil

The therapeutic efficacy of evening primrose oil, fish oil, borage oil, and their constituent components has been evaluated in a number of studies. Several randomized controlled trials were available for detailed review; however methodologies varied, as did supplement dosages and control procedures.[119-121,122] Sample size ranged from 48 to 160 patients and duration of treatment ranged from 12 to 24 weeks. Two of the studies enrolled only adult patients.

Berth-Jones and Graham-Brown (1993) evaluated the effect of dietary supplementation with evening primrose oil alone and in combination with fish oil in a randomized, double-blinded trial involving patients diagnosed with moderate-to-severe AD[118] according to the criteria of Hanifin and Rajka.[2] They found no significant therapeutic advantage for either treatment when compared to the control group.[118] Hederos and Berg (1996) similarly found no difference in effect between evening primrose oil and sunflower oil in 58 children studied.[119] However, another group compared the effect of supplementation with linoleic acid-containing sunflower oil, fish oil, and olive oil as placebo in 48 adults with AD, with results suggesting therapeutic efficacy for sunflower oil.[120] In a randomized trial, Henz et al. (1999) found no significant therapeutic effect of borage oil, compared with bland lipid placebo, for patients with AD.[121]

Evidence from the reviewed studies is summarized in the following table.

Table 6b.–Summary of Studies of Evening Primrose Oil, Borage Oil, and Fish Oil in the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; f/u, follow-up; grp(s), group(s); NR, not reported; pt(s), patient(s); RCT, randomized controlled trial; tx(s), treatment(s)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/Limitations
I	**Berth-Jones and Graham-Brown, 1993[118]** Double-blind, randomized parallel study to evaluate the effect of dietary supplementation with evening primrose oil and/or fish oil on the extent and severity of AD symptoms	123 pts (adult and pediatric) with moderate-to-severe AD were randomized to receive daily 6 capsules of one of the following for 16 wks: Evening primrose oil containing linoleic and gamma-linoleic acid (n=33) Evening primrose oil containing linoleic and gamma-linoleic acid and fish oil containing icosapentanoic acid and docosahexanoic acid (n=35) Liquid paraffin (adults) or olive oil (children) placebo (34) 102 subjects completed the study Subjects were examined at 4, 8, and 16 wks of tx, and after 8-wk washout	Severity of AD was measured using the scoring system developed by the authors and also the Costa scoring system Extent of skin involvement was evaluated using the rule of nines Topical steroid use was monitored by weighing returned tubes of medication	Neither tx was associated with greater clinical improvement than that seen in the placebo grp All 3 grps used less topical steroid medication, with the largest reduction in the placebo grp	Rigorous diagnostic and severity assessment criteria used by blinded evaluators. Large sample size, lengthy tx period. 17 pts dropped out during the study, 8 due to deterioration of AD. *Limitations:* Pts continued to use varying amounts and potencies of topical corticosteroids and antihistamines during the study
I	**Hederos and Berg, 1996[119]** RCT to evaluate the effect of evening primrose oil on the severity of AD and asthma	58 children were randomized to receive 500 mg daily of one of the following for 16 wks: Evening primrose oil containing 40 mg gamma-linoleic acid (n=29) Sunflower oil placebo (n=29) All pts received their usual topical and systemic tx	Severity of AD was evaluated using a visual analog scale and grading of signs and symptoms combined with a global assessment made by a blinded clinician	Both tx and control grps improved over course of study. No significant differences were seen between grps.	*Limitations:* Grading of symptoms done using nonvalidated methods

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/Limitations
I	**Giménez-Arnau et al., 1997[120]** RCT to evaluate the effect of dietary fatty acid supplementation on extent and severity of AD symptoms in adults and measure fatty acid metabolites	48 adult pts with moderate-to-severe AD were randomized to receive 3 g daily of one of the following dietary supplements for 3 mos: Sunflower oil containing linoleic acid (n=16) Fish oil containing icosapentanoic acid (n=16) Olive oil containing oleic acid (placebo) (n=16) Numbers completing study in each grp NR Pts were evaluated after 6 and 12 wks of tx	Severity and extent of disease assessed using Rajka score and rule of nines Fatty acid metabolites quantified by laboratory measurement	Pts in the linoleic acid supplementation grp had a significant reduction in the severity of AD	Validated criteria used for dx and evaluation. Blinded evaluations. *Limitations:* Small sample size
I	**Henz et al., 1999[121]** RCT to evaluate the effect of dietary supplementation with high gamma-linoleic acid borage oil on extent of severity of AD	160 adult pts with moderate AD were randomized to take daily for 24 wks 500 mg of one of the following: Borage oil (n=80) Bland lipid placebo (n=80) Moderate-potency steroid cream was provided to all pts to be used only as necessary Clinical status, tolerability, compliance, and corticosteroid use were assessed at wks 1, 2, 6, 12, 18, and 24	Disease activity assessed using Costa score. Use of corticosteroid cream was estimated from pt records.	No significant differences were seen in disease activity or use of steroids between the 2 grps in the multicenter study	Some subgrps showed a trend toward positive response to tx, but these did not reach statistical significance Adverse events were reported by 27 pts in tx and 28 pts in control grps

Pyridoxine, vitamin E and multivitamins, and zinc supplementation
No clinical trials investigating the role of vitamin E or multivitamins in the treatment of AD were available for review. Only one trial reported on a randomized, double-blind, placebo-controlled study using 50 mg pyridoxine hydrochloride as a daily treatment for 19 children for 4 weeks. No differences in AD severity or extent of disease were found when compared with 22 age- and severity-matched controls.[123] Similarly; Ewing et al. (1991) performed an 8-week double-blind trial of oral zinc supplementation in the treatment of AD in a population of 50 children, and saw no therapeutic benefit.[124]

Probiotics
Probiotic therapy may be of benefit in the treatment of AD. Attention to optimum dosing, efficacy, safety and duration of therapy need to be further established and independent confirmation is needed. [16] It is unclear whether lactobaccillus preparations commercially available in the US would affect the same results.

Summary

Although there is some evidence that avoidance of foods to which a patient has a known sensitivity may reduce the severity and extent of AD, the reintroduction of these foods often is not clearly associated with exacerbations. This makes it difficult to confirm the involvement of a specific food in the AD disease process for the individual patient or to establish causality. Evidence regarding the role of exclusive breast-feeding suggests that this has little protective or therapeutic effect.

There is little evidence to indicate that dietary supplementation with evening primrose oil, borage oil, or fish oil is of therapeutic value in the treatment of AD. Most studies enrolled patients who continued to use various topical and systemic medications, which may have confounded interpretation of study results. Even so, therapeutic value has not been demonstrated for these substances, even for their use as adjunctive therapy. Dietary supplementation with pyridoxine, vitamin E and multivitamins, and zinc as a treatment modality for AD is similarly unsupported by the peer-reviewed medical literature.

7. **What is the effectiveness of nonpharmacologic approaches such as house dust mite reduction, avoidance of enzyme-enriched detergents, specialized clothing, salt baths, nurse education, bioresonance, psychological approaches and ultraviolet (UV) phototherapy, for the treatment of atopic dermatitis?**

House dust mite reduction

Several studies of the effect of house dust mite reduction were identified in the peer-reviewed literature. One investigation confirmed that the amount of house dust mite antigen in airborne particles can be reduced in specially prepared hospital rooms, and noted a significant decrease in symptoms for patients with high house dust mite-specific immunoglobulin E (IgE) levels treated in such "clean" rooms.[125] Tan et al. (1996) found that mattress covers substantially reduced dust collected from mattresses, but reported little evidence of reduction of the symptoms of atopic dermatitis (AD) in his small study population.[126] The results of this study were also reported by Friedmann and Tan (1998).[127]

A small group of pediatric patients in a randomized controlled study experienced significant improvement in AD severity after reduction in house dust mite allergen in their home environments,[128] although this result was not replicated in a group of adult patients.[129] Use of occlusive bedding was also studied by Holm et al. (2001), who attempted to identify patient subgroups for whom this therapy would be most effective, and found no differences between treatment and control groups.[131] This was also studied by Koopman with the same lack of demonstrated effect.[130]

Evidence from the reviewed studies is summarized in the following table.

Table 7a.–Summary of Studies of House Dust Mite Reduction in the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; f/u, follow-up; grp(s), group(s); IgE, immunoglobulin E; pt(s), patient(s); RCT, randomized controlled trial; tx(s), treatment(s)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
I	**Tan et al., 1996[126]** RCT to evaluate the effect of house dust mite allergen elimination measures on the severity of AD symptoms	60 adult and pediatric pts who had ≥1 immediate response to a skin-prick challenge with a range of aeroallergens were randomized to one of the following for 1 yr: Active tx designed to eliminate house dust mite antigens in the home (n=30) Sham tx placebo (n=30) 48 pts competed the study Pts were evaluated and house dust samples collected at baseline and monthly for 6 mos	Extent and severity of AD evaluated by 1 blinded clinician using rule of nines and a six-area total-body severity assessment House dust mite antigen from house dust samples was isolated and quantified	Final mean area affected by AD was decreased in both tx and control grps. In adults pts there was no difference between the 2 grps. Children in the tx grp had significantly greater reduction in extent of AD than the placebo grp. The weight of dust collected from tx grp mattresses fell by 98% in the 1st mo and remained stable thereafter. No correlation was found between the dust loads and severity of symptoms	Pts were allowed to use their full range of normal txs. Dust mite antigen was found in all carpets at the end of the study. *Limitations:* Small sample size

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
I	**Ricci et al., 2000[128]** RCT to evaluate the effect of house dust mite allergen elimination measures on the severity of AD symptoms	41 pediatric pts with AD and high total and/or specific IgE levels were randomized to one of the following for 2 mos: Allergy avoidance measures such as encasing pillows and mattresses in microfiber covers, weekly washing of bedding, frequent vacuuming (n=20) Usual housekeeping control (n=20) Pts were evaluated and dust from beds was sampled and quantified at baseline, 1 mo, and 2 mos	Clinical severity evaluated using SCORAD index. House dust mite antigen from house dust samples was isolated and quantified.	Both grps improved compared to baseline. Significant reduction in severity of AD symptoms in the tx grp. Dust mite load decreased significantly in the tx grp after the 1st mo, and again after the 2nd mo, but did not decrease thereafter	Use of topical steroids and oral antihistamines were allowed for acute relapse of AD Validated diagnostic criteria and scoring method used for evaluating extent and severity of AD symptoms After the 2-mo study the avoidance measures were offered to all pts for 10 mos. Dust mite load was similarly reduced for these pts. *Limitations:* Small sample size
I	**Holm et al., 2001[131]** RCT to evaluate the effect of house dust-mite allergen elimination measures on the severity of AD symptoms	40 adult pts with AD were randomized to one of the following txs: Polyurethane-coated mattress cover (n=22) Plain cotton mattress cover control (n=18) Dust samples were collected at baseline and after 3, 6, 9, and 12 mos. Pts were evaluated and IgE levels were determined at baseline and after 1, 2, 3, 6, and 12 mos.	Clinical severity evaluated using SCORAD index. Pruritus severity self-reported. House dust mite allergen antigen from house dust samples was isolated and quantified. Allergen sensitization determined by laboratory assay of IgE levels.	Severity of AD symptoms was significantly reduced in both tx (45%) and control grps (39%). Pruritus also decreased significantly for both tx and control grps. House dust mite exposure decreased significantly in tx grp IgE levels decreased significantly in tx grp	Pts not sensitized to house dust mite antigen benefited as much from the occlusive bedding as did sensitized pts. *Limitations:* Small sample size

Avoidance of enzyme-enriched detergents
One investigation of the effect of enzyme-enriched detergents on symptoms of AD, a blinded crossover trial of 25 adult patients, was identified.[132] Although the diagnostic criteria used by the investigators were not described; the SCORAD (SCORing Atopic Dermatitis) index was used in evaluation of the patient population. No statistical differences in symptomatic relief were found between patients who used enzyme-enriched detergents and those who used a control detergent without enzyme enrichment.

Specialized clothing
No clinical trials investigating the efficacy of specialized clothing in the treatment of AD were identified in the peer-reviewed literature.

Salt baths
No robust clinical trials of the efficacy of salt baths were identified in the peer-reviewed literature. A single report of an investigation of bacterial colonization reported significant reduction of *Staphylococcus aureus* in skin cultures of AD patients whose symptoms were reduced following acidic hot-spring bathing.[133]

Nurse education
Two publications describing investigations of the clinical effect of education of parents of AD patients by a nurse were available for analysis. In an unblinded study by Broberg et al. (1990), the intervention involved both education and demonstration of therapy, and a questionnaire completed by the patients' parents was supplemented by a documented severity grading system. Significant improvement in the patients' clinical condition was associated with increased use of prescribed topical corticosteroid therapy.[134] In a recent randomized controlled trial, Chinn et al. (2002) evaluated the effect of a single educational session conducted by a dermatology nurse on quality of life in children with AD. This study enrolled 235 children, with follow-up at 4 and 12 weeks after the educational session. There was little impact of this educational session on quality-of-life measures, although the authors noted that the study had low statistical power for some outcome measures, and therefore may have failed to detect small treatment effects.[135]

Bioresonance
No clinical trials investigating the efficacy of bioresonance in the treatment of AD were identified in the peer-reviewed literature.

Psychological approaches
A small number of preliminary studies of the effect of psychological treatment modalities, including behavior modification and stress reduction techniques, were identified in the peer-reviewed medical literature and available for review. Most found significant benefits associated with group psychotherapeutic treatments. All focused on relaxation techniques and some utilized behavior modification techniques, thought to be potentially valuable in reducing the exacerbation of AD symptoms caused by scratching.[136]

Cole (1988) treated a group of 10 patients with chronic AD who had previously used systemic therapy for exacerbations for 12 weeks, using a ten-point program including relaxation and behavioral therapies. This study found that the average extent and severity of AD symptoms were significantly reduced for this small group, and that their use of topical corticosteroids also decreased significantly.[137] In 1989, a report of a pilot study of 3 patients, who received individual therapy emphasizing

relaxation and cognitive-behavioral techniques, found that these patients, who had been severely disabled by their skin disease, were greatly improved and able to control skin symptoms with topical medications. This effect persisted for up to 2 years.[138]

In a randomized, blinded study of 124 adult patients, Ehlers et al. (1995) compared the effect of adding four kinds of group treatments to standard medical care for treatment of AD. These group treatments consisted of dermatitis education, relaxation training, behavioral therapy, including both cognitive and relaxation elements, and a combination of education and behavioral therapy.[139] Using validated diagnostic criteria[2] and a well-described scoring system, this study found that 1 year after treatment, patients who received the psychological treatments (relaxation training and behavioral therapy) had a significantly greater improvement in AD symptoms than did those patients who received dermatitis education plus standard medical care or medical care alone.

UV phototherapy

A relatively large number of reports on the effect of ultraviolet (UV) phototherapy, including studies of chemophototherapy using methoxypsoralen (PUVA therapy) were identified in the peer-reviewed literature, although only a few were randomized controlled clinical trials. Several small, uncontrolled studies evaluated safety and efficacy parameters for UV phototherapy using specific wavelengths and equipment.[140-142]

In a description of the results of the treatment of patients of at least 13 years of age, Ogawa and Yoshiike (1992) described the results of daily topical PUVA therapy in 114 AD patients 13 years of age and older. Most patients in this series experienced substantial improvement in symptoms, and use of topical corticosteroid was significantly reduced.[143] Sheehan et al. (1993) achieved similar results in an open study of the treatment of 53 children 6 to 16 years of age, achieving complete or near-complete skin clearing lasting a year or more for 39 patients. These authors specifically noted the absence of adverse effects and the tolerability of the treatment for these young patients.[144] The safety of long-term therapy was addressed by Morris and Saihan (2002), who reported on 11 patients, some of whom had received more than 150 PUVA treatments in over 7 years.[145]

The improved acceptability of narrow-band UVB phototherapy was documented by Collins and Ferguson (1995), who reported that half of their pediatric patients who experienced remission of symptoms with UVB therapy relapsed within 3 to 4 months, and that another 25% relapsed 6 to 9 months after therapy was discontinued.[146] Hudson-Peacock et al. (1996) reported the results of narrow-band UVB phototherapy in the treatment of 37 adult and pediatric patients.[147] Although difficulties with accurate assessment of improvement in patients with severe AD were noted, the results were similar to previous reports.

Krutmann et al. (1998) evaluated the efficacy of high-dose UVA1 therapy (wavelength 340-400 nm) for patients with severe AD. In a randomized, multicenter study, UVA1 phototherapy was compared with topical moderate-potency corticosteroid therapy and with conventional UVA-UVB phototherapy in 53 patients hospitalized due to acute exacerbations of severe chronic AD.[148] High-dose UVA1 was associated with significantly greater improvement in severity scoring than corticosteroid, and both UVA1 phototherapy and corticosteroid therapy were superior to UVA-UVB therapy. Concerned over the environmental heat produced by

conventional UVA1 therapy, von Kobyletzki et al. (1999) studied a filter system that allows cooler conditions during treatment.[149] Although 5 of the 50 adult patients treated with the heat-producing therapy did not complete the study, citing discomfort with the treatment, the results of both the conventional UVA and cool-light UVA were similar and slightly better than those achieved with UVA-UVB therapy. A similar therapeutic regimen was offered to 32 patients by Abeck et al. (2000), who noted significant improvement in mean SCORAD scores, but also documented loss of this benefit within 3 months of ending treatment.[150] Reynolds et al. (2001) documented significantly greater benefit to patients treated with narrow-band UVB compared with UVA, and noted that this difference persisted to a small extent for 4 months.[151]

Optimal UVA1 dosage was addressed by a descriptive report that documented similar therapeutic results and duration of benefit in patients receiving high-and medium-dose treatment. A rapid relapse rate, similar in both groups studied, was also described by this investigation.[152]

Two small descriptive studies of extracorporeal phototherapy involving UVA extracorporeal irradiation of enriched lymphocytes in the presence of methoxypsoralen reported clinical remission of severe refractory disease after a few sessions, and maintenance of therapeutic effect with prolonged treatment intervals.[153,154]

Table 7b.–Summary of Studies of Phototherapy in the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; F/u, Follow-up; grp(s), group(s); nm; nanometers; PUVA, psoralen phototherapy; pt(s), patient(s); RCT, randomized controlled trial; SCORAD, SCORing Atopic Dermatitis; tx(s), treatment(s) or therapy(ies)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
I	**Krutmann et al., 1998[148]** RCT to compare the effect of UVA1 phototx (wavelength 340-400 nm) with topical corticosteroid tx and UVB-UVA phototx for tx of acute exacerbations of AD	53 adult pts hospitalized for acute exacerbations of severe AD were randomized to receive one of the following for 10 days: High-dose UVA1 phototx (n=20) Topical tx using moderate-potency corticosteroid cream or ointment (n=17) UVA-UVB phototx (n=16) All pts completed the study Pts were evaluated at baseline and after 5 and 10 days of tx	Clinical severity of AD was assessed using the scoring system of Costa	All three grps improved significantly. At the completion of tx, pts in the UVA1 grp had significantly better results than topical corticosteroid grp or UVA-UVB grp.	Validated diagnostic and severity criteria described Additional tx was restricted for all tx grps to emollients only No serious side effects were noted in any pts *Limitations:* Hospitalized pts
I	**von Kobyletzki et al., 1999[149]** RCT to compare effect of conventional UVA1 (340-400 nm) tx with that of cool-light UVA1 (a system designed to provide tx with lower ambient temperatures) and with UVA-UVB tx for tx of AD symptoms	120 adult pts with severe AD were randomized to receive one of the following 5x/wk for 3 wks: Conventional UVA1 tx (n=50) Cool-light UVA1 tx (n=50) UVA-UVB tx (n=20) 108 pts completed the study Pts were evaluated at baseline, after 3 wks of tx, and 4 wks after completion of tx	Severity of AD was assessed by a blinded observer using SCORAD scoring system	All pts experienced significant improvement. The results of both the conventional UVA and cool-light UVA were similar and slightly better than those achieved with UVA-UVB tx. Pts receiving UVA tx had more prolonged effect when examined at f/u 4 wks after tx ended	Validated diagnostic and severity scoring criteria described 5 pts in conventional UVA discontinued tx due to heat experienced during tx

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
I	**Reynolds et al., 2001**[151] RCT to compare the effect of narrow-band UVB with UVA and with visible light for the tx of AD symptoms	69 adult pts with moderate-to-severe AD were randomized to receive one of the following 2x/wk for 12 wks: Narrow-band UVB tx (n=24) UVA tx (n=23) Visible light tx (n=22) 47 pts completed the study	Reduction in total disease activity measured by blinded investigators rating symptoms at 6 body sites on 0-3 scale	Mean reduction in symptom scores after 24 txs was significantly greater for UVB grp compared to UVA grp. 4 mos after tx, pts in UVB grp experienced fewer AD symptoms, but this was not significantly greater than UVA pts. Both grps experienced significantly greater reduction in severity compared to visible light grp.	Validated diagnostic used *Limitations:* High dropout rate (32%)

Summary

Although several authors have attempted to elucidate the role of allergen avoidance in the treatment of AD, there is no conclusive evidence that this intervention is effective for most patients with AD. There is also insufficient evidence in the peer-reviewed literature to conclude that avoidance of enzyme-enriched detergents, specialized clothing, salt baths, or bioresonance has a clinically beneficial effect on symptoms of AD.

Preliminary studies have provided conflicting results regarding the effect of a single educational session provided for parents of AD patients. Education about dermatitis and its manifestations and management have also been incorporated into psychotherapeutic approaches to the treatment of AD, and results, although extremely limited, are uniformly positive for a combination of educational and psychological interventions.

UV phototherapy, including UVA, UVB, and PUVA therapy, is well established in the treatment of AD, although rapid relapse following cessation of therapy has been noted. The safety of long-term maintenance through attenuated therapy is supported by evidence from clinical investigations.

8. **What is the effectiveness of systemic immunomodulatory agents such as desensitization injections, tumor necrosis factor inhibitors such as Enbrel® (etanercept) and Remicade® (infliximab), allergen-antibody complexes of house dust mites, leukotriene inhibitors, Cyclosporin A, interferon-gamma, thymopentin (TP-5), intravenous immunoglobulin (IVIG), azathioprine, methotrexate, mycophenolate mofetil, prednisone, and oral Elidel® (pimecrolimus or ascomycin), theophylline and papaverine for treatment of atopic dermatitis?**

Systemic immunomodulatory agents have been studied in recent years generally as therapy for refractory atopic dermatitis (AD) that does not respond to topical therapies.[155] Some systemic immunomodulatory agents, such as cyclosporin have been extensively studied in randomized controlled trials. Others, such as intravenous immunoglobulin and gamma-interferon, have been investigated in only a small number of studies and there is insufficient evidence to evaluate efficacy or safety adequately. There are also medications such as etanercept and infliximab that have shown early promise in the treatment of psoriasis, for which there is no published clinical evidence regarding their use in the treatment of AD. Finally, prednisone, though commonly used in the treatment of refractory AD, has not been systematically and rigorously evaluated for efficacy or safety for this indication.

Desensitization injections

Only one randomized controlled clinical trial of the effect of hyposensitization therapy in the treatment of AD was available for analysis. Glover and Atherton (1992) described the results of a trial in which 24 children with AD and immediate hypersensitivity to house dust-mite antigen were randomized to receive either a standard 8-month course of desensitization injections or placebo. A significant benefit of desensitization was not demonstrated.[156]

Tumor necrosis factor (TNF) inhibitors such as Enbrel® (etanercept) and Remicade® (infliximab)

No clinical trials of etanercept or infliximab for the treatment of AD were identified in the peer-reviewed literature.

Allergen-antibody complexes of house dust mites

A small number of clinical trials evaluating the effect of injection of house dust mite antigen-antibody complexes were identified in the peer-reviewed medical literature. All four studies available for review were performed by the same group of investigators, involved small patient populations, and enrolled adult patients with demonstrated sensitivity to house dust mite antigen.[157-160] Leroy et al. (1991) reported an open trial of 10 patients who received injections of allergen-antibody complexes.[157] This study used valid diagnostic criteria for AD[2] and documented rapid and significant improvement in patients, but also noted some loss of efficacy toward the end of a year of treatment. In a larger randomized placebo-controlled trial,[158] interim results indicated rapid improvement in both treatment and placebo groups until 8 weeks of therapy had been completed, after which time the patients who received antigen-antibody complex injections showed significantly greater reduction in AD symptoms than those given placebo. A second trial by this same group reported similar results, and also noted occasional flares of pruritus and other disease activity in both treated and control group patients.[159] These investigators later obtained significant reduction of disease in 8 patients using antibody fragments for preparation of antibody-allergen complexes.[160] Evidence from the reviewed studies is summarized in the following table.

Table 8a.–Summary of Studies of Injection of Allergen-Antibody Complexes in the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; f/u, follow-up; grp(s), group(s); pt(s), patient(s); RCT, randomized controlled trial; tx(s), treatment(s) or therapy(ies)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/Limitations
I	**Leroy et al., 1992[158]** RCT to evaluate effect of injection with allergen-antibody complexes for tx of AD	23 adult pts with AD and demonstrated sensitivity to house dust mite antigen were randomized to receive one of the following for 4 mos: Injection of individually prepared house dust mite antigen-antibody complexes (n=12) Injection of carrier buffer placebo (n=11) 22 pts completed the study Pts were evaluated wkly during the first 4 mos of tx, then monthly for 4 additional mos	Global assessment of severity determined by multiplying of symptom scores as 6 body sites by estimated body surface area involved	73% of pts demonstrated clinical improvement after injection of antigen-antibody complexes. The therapeutic benefit was durable for up to 8 mos with maintenance tx	Valid diagnostic criteria utilized for enrollment of pts. Scoring of severity and extent of AD symptoms using described system. Placebo grp pts were offered active tx after the original study was completed, and demonstrated similar improvement in symptoms *Limitations:* Small sample size
I	**Leroy et al., 1993[159]** RCT to evaluate effect of injection with allergen-antibody complexes for tx of AD	24 adult pts with AD and demonstrated sensitivity to house dust mite antigen were randomized to receive one of the following for 4 mos: Injection of individually prepared house dust mite antigen-antibody complexes (n=12) Injection of carrier buffer placebo (n=12) After 4 mos, placebo-tx pts received active tx 23 pts completed the study Pts were evaluated wkly during the first 4 mos of tx, then monthly for 4 additional mos	Global assessment of severity determined by multiplying of symptom scores as 6 body sites by estimated body surface area involved	Symptoms subsided for most pts within a few wks of beginning tx, and at 1 yr after tx began; 82% of pts experienced a mean improvement of 83% Wheal and flare reaction was noted at the injection site in most pts	Pts were admitted to the study over an extended time period to avoid the effect of seasonal exacerbation of AD symptoms. Topical 0.5% prednisolone cream, oral steroids, and oral antihistamines were allowed during the study period. *Limitations:* Small sample size

Leukotriene inhibitors
There have been a small number of clinical investigations into the use of leukotriene inhibitors for the treatment of AD. The studies available for analysis all involved small study populations. Validated diagnostic criteria were used by all investigators for enrollment of patients, but medications, dosages, and lengths of treatment varied among studies. Both pediatric and adult populations were studied. In a pilot study, Woodmansee and Simon (1999) administered 600 mg of zileuton four times a day to 6 adults with moderately severe AD. Other medications were discontinued. Mean symptom severity score decreased compared to baseline assessments in this small study.[161] Another pilot study utilizing a crossover design treated 11 children with 5 mg montelukast daily for 4 weeks. In this study, more severely affected patients demonstrated significant reduction in disease severity.[162] Another crossover study of 8 adult patients reported a small, but significant, reduction in symptom severity when treated for 4 weeks with 10 mg montelukast daily.[163] A single-blind study of 32 adult patients that used validated enrollment and scoring criteria concluded that 6 weeks of therapy with 10 mg daily of montelukast was equivalent in efficacy to a combination therapy using antihistamines and topical corticosteroids.[164]

Cyclosporin A
A large number of clinical trials of cyclosporin for treatment of symptoms of AD have been published in the peer-reviewed medical literature. Small, early trials that demonstrated prompt relief of symptoms with rapid relapse after cessation of treatment[165] were succeeded by studies of long-term maintenance therapy[166] and documentation of a clinically observable therapeutic effect, without evidence of altered immune response.[167] In a double-blind randomized controlled trial involving adult AD patients, treatment with 5 mg/kg/day cyclosporin was associated with a significant reduction in symptom scores compared with placebo, but also with significantly more adverse events, although no patients withdrew from the study.[168] Measurement of patient-reported quality of life in this same group of patients indicated that the treatment produced improved quality of life for patients, which appeared to persist after cessation of treatment and reappearance of symptoms.[169]

Long-term therapy was further investigated in a study of 19 patients in which satisfactory maintenance of remission was maintained with cyclosporin dosages of 5 mg/kg every fifth day or 1 mg/kg/day.[170] van Joost et al. (1994) reported a similar excellent clinical effect in a larger randomized controlled trial involving treatment with 5 mg/kg/day for 6 weeks.[171] The treated group in this study had significant increases in values of serum creatinine and bilirubin, which returned to normal after the treatment ended, and this study was also compromised by a very high rate of discontinuation by control group patients. Granlund et al. (1995), in a study of time to relapse after treatment, reported that 75% of a group of 43 patients successfully treated with cyclosporin for 6 weeks relapsed after 2 weeks without treatment, and 90% relapsed to pretreatment disease severity after 6 weeks.[172]

Berth-Jones et al. (1996) treated 27 children with severe AD with 5 mg/kg/day of cyclosporin for 6 weeks.[173] Significant improvements in all measures of disease activity were seen in all patients, with marked improvement or total clearing reported for 22 patients. Time to relapse was reported as variable in this group, although most patients relapsed within a few weeks. Chawla et al. (1996) confirmed the equivalent clinical efficacy and superior pharmacokinetics of the newer microemulsion formulation, Neoral®, and noted a trend toward fewer reports of adverse effects in a study in which patients received between 3 and 5 mg/kg/day of the active drug.[174]

An open study of 18 pediatric patients (Zaki et al., 1996) reported excellent results and very few side effects of therapy, with a highly variable time to relapse after 6 weeks of treatment.[175] In an open dose-ranging study that reported a very high dropout rate, the most common side effects related to treatment were hypertension, hypertrichosis, paresthesias, and vomiting, with a cyclosporin dosage of 3.7 mg/kg/day required to maintain efficacy.[176] In a long-term dose-ranging study, Berth-Jones et al. (1997) found that a cyclosporin dosage of 3 mg/kg/day was sufficient to produce and maintain highly significant reduction in symptom severity in adult patients with AD, and was well tolerated for up to 48 weeks.[177]

Harper et al. (2000) compared the effect of short-course cyclosporin therapy with continuous therapy in a group of 40 children, 29 of whom completed the 12-week study.[178] Both treatment groups had similar results, with a significantly lower average total medication dosage reported for the group on short-course therapy. A later study of 10 children identified 7 as "responders" to 8 weeks of therapy with 2.5 mg/kg/day of cyclosporin microemulsion, reporting no relapse in these patients 4 weeks after treatment ended.[179]

Evidence from the reviewed studies is summarized in the following table.

Table 8b.–Summary of Studies of Cyclosporin A in the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; f/u, follow-up; grp(s), group(s); pt(s), patient(s); RCT, randomized controlled trial; tx(s), treatment(s)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
I	**Sowden et al., 1991**[168] RCT to assess the efficacy and safety of cyclosporin for the tx of AD	33 pts with severe refractory AD were randomized to receive one of the following: Cyclosporin (5 mg/kg/day) for 8 wks, followed by placebo for 8 wks (n=17) Placebo for 8 wks, followed by cyclosporin (5 mg/kg/day) for 8 wks (n=16) All pts completed the study Pts were evaluated at baseline and every 2 wks	Severity of AD was graded by blinded clinicians based on a six-area 0-3 scale. Extent of AD was estimated by "rule of nines". Pts reported itch and sleep scores. Topical steroid use was estimated by weighing returned tubes of medication.	Significant improvement in AD symptoms occurred within 2 wks of beginning tx. Relapse of symptoms occurred within 2 wks of ending tx. Topical steroid use was significantly reduced in tx grp. 20 pts in the tx grp reported 39 adverse events, compared with 8 pts reporting 8 adverse events in the control grp. Nausea, abdominal pain, and paresthesias were most commonly reported.	Valid diagnostic criteria used in pt selection. Severity scoring system described and illustrated. *Limitations:* Relatively small sample size
I	**van Joost et al., 19941**[171] RCT to assess the efficacy and safety of cyclosporin in the tx of AD	46 adult pts with severe refractory AD were randomized to receive one of the following for 6 wks: Cyclosporin (5 mg/kg/day) (n=23) Placebo (n=23) 28 pts completed the study Pts were evaluated at baseline and every 2 wks	Severity of AD was graded by blinded clinicians based on a six-area 0-3 scale. Extent of AD was estimated by "rule of nines". Pts reported itch and sleep scores.	Pts in tx grp had significant reduction in AD symptoms Tx grp had significant increases in values of serum creatinine and bilirubin, which returned to normal after tx period 2 pts in tx grp developed hypertension	*Limitations:* Relatively small sample size; 61% control grp dropped out of study

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
II-3	**Berth-Jones et al., 1996[173]** Open study to assess the safety and efficacy of cyclosporin in tx of AD	27 children (mean age 9 yrs) with severe AD received 5 mg/kg/day Cyclosporin in 2 divided doses All pts completed the study Pts were evaluated at baseline and every 2 wks	Severity of AD was graded by clinicians based on a six-area 0-3 scale. Extent of AD was estimated by "rule of nines". Parents of pts reported sleep, itch, and irritability scores on a visual analog scale. Topical corticosteroid use was estimated by parents.	Most pts experienced marked to total clearing of AD symptoms, improved quality of life, and reduction in topical corticosteroid requirement 16 pts reported 33 adverse events during tx. The most commonly reported adverse effect was headache, present in 4 pts prior to tx.	25 pts and families considered the tolerability of this drug good or very good *Limitations:* Uncontrolled open study; small sample size
II-3	**Zonneveld et al., 1996[176]** Randomized open study to determine the optimum dosing schedule with regard to the efficacy and safety of cyclosporin in the tx of AD	78 adult pts with severe long-standing AD were randomized to receive one of the following for 2 mos: Oral cyclosporin 5 mg/kg/day, decreasing to 3 mg/kg/day if satisfactory response maintained (n=38) Oral cyclosporin 3 mg/kg/day, increasing to 5 mg/kg/day until satisfactory response maintained (n=40) 30 pts completed the study Optimal dose maintained for 10 additional mos Tx stopped after 28 days if no favorable response to highest dose observed Pts were evaluated every 2 wks for 2 mos, then monthly	Severity of AD was graded by clinicians based on a six-area 0-3 scale. Extent of AD was estimated by "rule of nines". Overall efficacy of tx was rated by investigator and pt.	Mean dosage of cyclosporin was 3.7 mg/kg/day in both grps at the end of the 2-mo study period. Symptom severity scores decreased significantly in most pts; no significant difference in efficacy or safety in the two different dosage schedules. A very high rate of adverse events occurred, principally hypertension, hypertrichosis, paresthesias, and vomiting	*Limitations:* Extremely high (61%) dropout rate. Lack of efficacy, side effects, and noncompliance were cited as reasons for this.

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
II-3	**Berth-Jones et al., 1997[177]** Prospective open study to investigate the safety and efficacy of long-term tx of AD with cyclosporin	100 adult pts were enrolled and received oral cyclosporin, beginning at 2.5 mg/kg/day, adjusted according to skin response, for 48 wks 65 pts completed tx Pts were evaluated after 2 and 4 wks of tx, then monthly	Severity of AD was graded by clinicians based on a six-area 0-3 scale. Extent of AD was estimated by "rule of nines". Pts reported pruritus and sleep disturbance on a 0-3 scale. Global assessment at completion of study on 6-point scale by pts and investigators.	Most pts experienced rapid and highly significant reduction in disease severity. Most pts relapsed within 6 wks of cessation of tx. Mean dose necessary to improve symptoms was 3 mg/kg/day. 14 subjects withdrew from the study due to adverse effects. Gastrointestinal complaints and headache were the most common side effects.	Topical corticosteroids and antihistamines were used as required *Limitations:* Diagnostic criteria not described; 35% dropout rate

Interferon-gamma

Several studies that investigated the use of interferon-gamma in the treatment of AD were identified in the peer-reviewed medical literature. Most were small descriptive studies; however, three randomized, controlled clinical trials were available for review and analysis.

Hanifin et al. (1993) reported significant relief of AD symptoms in a relatively large study of children and adults treated for 12 weeks with subcutaneous injections of interferon-gamma, noting a high overall rate of adverse effects including flu-like symptoms, controlled with premedication.[180] Other small, open studies reported most or all patients showing marked clinical improvement after 4 to 6 weeks of therapy.[181,182] These authors noted no change in serum IgE concentrations and a highly variable time to relapse in their patients after cessation of therapy. Schneider et al. (1998) described similar clinical results of the treatment of a group of pediatric and adult patients with daily or alternate day injections of interferon-gamma for a minimum of 12 months, noting transient mild adverse effects and changes in laboratory parameters.[183]

Stevens et al. (1998) reported on the results of therapy with subcutaneously injected interferon-gamma for up to 22 months,[184] following patients whose short-term therapy was reported in an earlier publication.[180] The treatment effect of interferon-gamma was sustained, and long-term use was well tolerated by patients. In a dose-ranging study that investigated 12 weeks of interferon-gamma therapy, no difference between high-and low-dose therapy was detected.[186]

Evidence from the reviewed studies is summarized in the following table.

Table 8c.–Summary of Studies of Interferon-Gamma in the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; f/u, follow-up; grp(s), group(s); pt(s), patient(s); RCT, randomized controlled trial; SC, subcutaneous; tx(s), treatment(s) or therapy(ies)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
I	**Hanifin et al., 1993[180]** RCT to study the effects of recombinant human interferon-gamma for the tx of AD	83 pediatric and adult pts with moderate-to-severe AD were randomized to receive one of the following daily for 12 wks: SC injection of 50 μg/m^2 recombinant human interferon-gamma (n=40) SC injection of placebo (n=43) Pts were evaluated after 1, 4, 7, and 12 wks of tx 78 pts completed tx	Total clinical severity was assessed by clinicians using 0-3 scale on 6 body areas, evaluation of other symptoms, and pt report of therapeutic response	>50% improvement by clinician assessment seen in 45% of tx grp and 21% of placebo grp Significant response reported by 53% of pts in tx and 21% of pts in placebo grps Some symptoms showed significant improvement 30% of pts had transient fever and chills that lessened with time and premedication	Validated diagnostic criteria used for enrollment of pts A trend toward better response in pediatric pts did not reach statistical significance
III	**Stevens et al., 1998[184]** Case series to describe the effects of long-term tx with recombinant human interferon-gamma in the tx of AD	24 adult pts with moderate-to-severe AD who had responded to tx with wkly SC injections of 50 μg/m^2 recombinant human interferon-gamma continued in tx for up to 24 mos 16 pts completed the study Pts were assessed against baseline of original study and evaluated after 1 and 2 yrs of tx	Total clinical severity was assessed by clinicians using 0-3 scale on 6 body areas, evaluation of other symptoms, and clinical assessment of total clinical severity	All clinical parameters maintained significant reduction in severity compared to baseline. This was maintained after 1 and 2 yrs of tx Adverse effects related to tx included neutropenia, hepatic transaminase elevation, and flu-like syndrome. 1 pt dropped out due to side effects.	Validated diagnostic criteria used for enrollment of pts. Some severity grading criteria described. *Limitations:* Small study grp, open study

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
I	**Jang et al., 2000[186]** RCT to evaluate effect of high- and low-dose tx with recombinant human interferon-gamma in the tx of AD	51 adult pts with severe AD randomized to receive wkly tx with 1 of the following 3x/wk for 12 wks: Low-dose grp: SC injections of $0.5x10^6$ IU/m^2 of recombinant human interferon-gamma (n=20) High-dose grp: SC injections of $1.5x10^6$ IU/m^2 of recombinant human interferon-gamma (n=21) Placebo injections (n=10) 38 pts completed the study Pts were evaluated at baseline and after 2, 6, and 12 wks of tx	AD severity was measured by assessing 8 body areas and clinical estimation of total clinical severity. Extent of AD severity measured using "rule of nines".	Both tx grps showed significant reduction in disease severity compared to placebo grp. Although the high-dose grp improved more rapidly, the difference was absent after 12 wks of tx.	Validated diagnostic criteria used for enrollment of pts. Some severity grading criteria described. *Limitations:* Relatively small sample size in each tx grp; 25% dropout rate

Thymopentin

A small number of reports have been published in the medical literature that describe treatment of severe refractory AD with thymopentin (TP-5), a synthetic pentapeptide corresponding to five amino acid residues of the sequence of human thymopoietin. A randomized controlled trial involving 100 pediatric and adult patients reported significant improvement in patients who received subcutaneous injections of 0.5 mg of thymopentin daily for 6 weeks.[187] An open clinical trial of thymopentin therapy conducted with a group of 16 children that also investigated serum IgE levels noted significant clinical improvement after 3 weeks of treatment[188] although relapse occurred within 3 weeks of cessation of treatment. A 12-week trial of thymopentin in adolescents and adults with severe AD yielded no significant differences between the treatment and control groups in total severity scores, but significant improvement in physicians' assessment of overall improvement.[189]

Table 8d.–Summary of Studies of Thymopentin in the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; f/u, follow-up; grp(s), group(s); pt(s), patient(s); RCT, randomized controlled trial; tx(s), treatment(s)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
I	**Leung et al., 1990[187]** RCT to evaluate the effect of thymopentin for tx of AD	100 adult and pediatric pts with moderate-to-severe AD were randomized to receive one of the following daily for 6 wks: SC injections of 0.5 mg thymopentin (n=48) SC injections of placebo (n=52) 92 pts completed the study Pts were evaluated at baseline, after 1, 3, and 6 wks of tx, and 4 wks after ending tx	Blinded clinicians assessed 5 symptoms on a 0-3 scale. Pts kept a daily log of itch scores and topical corticosteroid use.	Significant reduction in mean symptom severity compared with baseline and control grp was seen in tx grp after 6 wks of tx. Topical steroid use was the same in both grps. Increase in symptom score was noted within 2 wks of cessation of tx. Similar numbers of adverse events were reported by both tx and control grps.	Validated diagnostic criteria used for enrollment of pts. Severity criteria scoring system described. *Limitations:* Brief f/u period
I	**Stiller et al., 1994[189]** RCT to evaluate the safety and efficacy of thymopentin as an adjunctive tx for AD	39 adolescent and adult pts with severe AD were randomized to receive one of the following 3x/wk for 12 wks: SC injection of thymopentin (n=20) SC injection of placebo (n=19) 35 pts completed the study All pts received placebo for 12 wks after tx ended 1.0% hydrocortisone cream, 0.1% triamcinolone cream, and antihistamines were dispensed by the study Pts were evaluated at baseline and on days 7, 21, 42, 63, 84, and 4 wks after tx ended	Clinicians rated 5 symptoms for severity on 0-3 scale. Pt and clinician reported overall assessments. Extent of disease evaluated using "rule of nines". Use of 0.1% triamcinolone and 1.0% hydrocortisone creams evaluated by weighing returned jars	No significant differences were seen in total severity scores between the 2 grps. No significant differences between the 2 grps were seen in serum IgE levels, use of topical corticosteroids, or use of antihistamines. No differences between the 2 grps were noted in the occurrence or type of adverse effects	Validated diagnostic criteria used for enrollment of pts. Severity scoring described. Significant reduction in severity of self-reported pruritus was noted in tx grp *Limitations:* Small sample size

Intravenous immunoglobulin
There have been very few clinical studies of the use of intravenous immunoglobulin (IVIG) for the treatment of AD. In an open study that investigated the safety and efficacy of 7 monthly infusions of 2 g/kg IVIG, there was no clear clinical benefit or any change in measures of immunological function found for 9 adult patients with severe AD.[190] In a controlled study, a single infusion of 0.5 g/kg IVIG or 15 g IVIG, depending on size, was administered to 40 patients with severe AD.[191] Significant reductions in severity scores compared to baseline and the control group were detected within 3 weeks of treatment.

Azathioprine
Very few clinical studies have been published on the immunosuppressive effect of oral azathioprine for the treatment of AD. [192, 193] Two reports of azathioprine therapy demonstrate effectiveness, but both were limited by high patient drop out rates secondary to side effects. [192, 193] The potential risks associated with long-term azathiprine use, including malignancy, have not been adequately investigated.

Methotrexate
No clinical trials of methotrexate for the treatment of AD were identified in the peer-reviewed literature.

Mycophenolate mofetil
Two clinical studies that investigated the efficacy of mycophenolate mofetil for the treatment of AD were identified in the peer-reviewed literature. Both of these open studies involved 10 adult patients with severe refractory AD and used validated diagnostic criteria and severity scoring systems.[2,4] In one study, patients were treated with 1 g of mycophenolate mofetil daily for 2 weeks, then the dose was increased to 2 g daily for 11 weeks longer. Both severity scores and serum IgE levels were significantly reduced after 4 weeks of treatment, and mean symptom severity scores continued to improve throughout treatment.[194] Grundmann-Kollman et al. (2001) treated patients with 1 g of mycophenolate mofetil daily for 4 weeks, then reduced the dose by half for 4 weeks, reporting significant reduction in symptom scores within 4 weeks. A small number of patients reported that this benefit was sustained for several months.[195]

Systemic Corticosteroids
Occasional short-term oral therapy with prednisone or intramuscular injections of triamcinolone acetonide is used to abort major exacerbations of AD symptoms.[155] Due to side effects, the potential for rebound flare of symptoms, and diminishing effects, it is used sparingly in adults and rarely in young children. No randomized controlled trials of prednisone therapy were identified in the peer-reviewed medical literature.

Oral Elidel®
No clinical trials of oral Elidel® for the treatment of AD were identified in the peer-reviewed literature.

Theophylline
One double-blind placebo-controlled crossover trial to evaluate the efficacy of oral theophylline for the treatment of AD was identified in the peer-reviewed medical literature.[196] In a brief report of this study, the authors did not describe the diagnostic criteria used and concurrent use of topical corticosteroid therapy was not addressed. Outcome measures in this study included patient-reported itch score,

sleep disturbance, amount of antihistamine used, and overall assessment of disease severity. There was no significant treatment effect of theophylline in this study; outcomes were similar after 300 mg/day theophylline and placebo.

Papaverine

Two double-blind randomized clinical trials of papaverine in the treatment of pruritus associated with AD were identified and reviewed. Berth-Jones and Graham-Brown (1990) investigated the efficacy of 400 mg papaverine per day compared with placebo in 50 adult patients with atopic dermatitis, monitoring symptoms and topical corticosteroid usage. No differences were found between papaverine and placebo groups for any parameters.[197] These results were confirmed by a smaller study with increasing doses, but a shorter treatment period.[198]

Table 8E.–Summary of Studies of Papaverine in the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; f/u, follow-up; grp(s), group(s); pt(s), patient(s); RCT, randomized controlled trial; tx(s), treatment(s)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/ Limitations
I	**Berth-Jones and Graham-Brown, 1990**[197] RCT to evaluate the effect of papaverine in the tx of AD	50 pediatric and adult pts with moderate-to-severe AD received one of the following 4x/day for 4 wks, followed by a 4-wk washout period, followed by the opposite tx: 100 mg (adults) or 60 mg (children) theophylline Placebo tablets 45 pts completed the study Pts were evaluated at baseline and after each tx period	Severity was evaluated by assessment of severity of 16 body areas on 0-3 scale. Pts reported itching on a visual analog scale 2x/day. Topical steroid use evaluated by weighing returned medication tubes.	There were no significant differences between the symptom scores of the active tx and placebo grps. Topical corticosteroid use did not change between active tx and placebo phases.	Validated diagnostic and severity criteria used for enrollment of pts. All pts continued to use topical emollient and corticosteroid tx, but no tx changes were allowed during study period.
I	**Shupack et al., 1991**[198] RCT to evaluate the effect of papaverine in the tx of AD	30 adult pts with stable AD were randomized to receive 1 of the following for 2 wks, then crossed over for 2 wks of the opposite tx: 150 mg papaverine 4x/day, increased to 300 mg 4x/day if no improvement Placebo 20 pts completed study Pts were evaluated at baseline and wkly	Pruritus was assessed by pts on 0-5 scale and estimate of the 100% of the day that pruritus was present. A specified lesion was graded for severity. Pts and physicians graded overall severity.	No statistically significant advantage of placebo over papaverine was demonstrated	Validated diagnostic and severity criteria not used for enrollment of pts or assessment of severity. Pts were allowed to use, but not change, normal topical tx. *Limitations:* Small sample size, short tx period

Summary

The evidence in the peer-reviewed medical literature does not support the use of desensitization injections for the treatment of atopic dermatitis.

Peer-reviewed clinical studies of the value of tumor necrosis factor inhibitors such as Enbrel® (etanercept) and Remicade® (infliximab) in the treatment of AD have not been performed. To date, there is no evidence to support their use in the treatment of AD.

Injection of allergen-antibody complexes of house dust mites has shown considerable efficacy in several relatively small studies of adult patients sensitive to the house dust mite antigen, but more investigation, involving larger groups of patients, is necessary to fully elucidate its role in the treatment of AD.

The available evidence does not currently support the use of leukotriene inhibitors in the treatment of AD. Additional study is needed to provide conclusive evidence to support the efficacy and safety of these compounds.

There is evidence in the peer-reviewed literature that oral treatment with cyclosporin is effective in reducing symptoms of AD in many children and adults. There is also evidence that this therapy is associated with a variable, but relatively rapid, relapse of symptoms following cessation of treatment. Optimal dosing and treatment schedules have not been completely elucidated.

There is some evidence that subcutaneous injection of interferon-gamma is an effective therapy for some patients with refractory AD. A significant number of side effects, notably flu-like syndrome, have been noted by investigators. Additional study is needed to provide conclusive evidence to support the optimum dosage.

Evidence in the peer-reviewed literature regarding the efficacy of thymopentin for the treatment of AD is limited and conflicting.

Evidence in the peer-reviewed literature regarding the safety and efficacy of IVIG for the treatment of AD is also limited and conflicting.

More clinical research is needed to adequately assess the role of oral azathioprine therapy in the treatment of AD, although preliminary results are encouraging.

Peer-reviewed clinical studies of the value of methotrexate in the treatment of AD have not been performed. To date, there is no evidence to support its use in the treatment of AD.

More clinical research is needed to adequately assess the role of oral mycophenolate mofetil therapy in the treatment of AD, although preliminary results are encouraging.

The peer-reviewed medical literature does not provide evidence for the safety and efficacy of the use of prednisone, theophylline or papaverine in the treatment of AD.

Peer-reviewed clinical studies of oral Elidel® for the treatment of AD have not been performed. To date, there is no evidence to support its use in the treatment of AD.

9. What is the effectiveness of complementary therapies such as Chinese herbs, homeopathy, hypnotherapy/biofeedback and massage therapy for treatment of atopic dermatitis?

Chinese herbs

A relatively large number of studies of the clinical effect of therapy with Chinese herbs on the symptoms of AD have been published. Although in traditional Chinese medicine, individual formulations are provided for each patient, there have been commercial combinations of Chinese herbs that have been proposed as effective in the treatment of AD. Formulations may differ in their herbal content, and Keane et al. (1999) published an analysis of 11 commercially available preparations that demonstrated that eight of them contained substantial amounts of dexamethasone.[199]

A randomized controlled trial by Sheehan et al. (1992) examined the safety and efficacy of a standardized preparation of Chinese herbs for the treatment of adults with severe AD. Significant reductions in erythema and extent of skin involvement were reported during 8-week treatment intervals.[200] This result was then replicated in a pediatric study population.[201] This pediatric study was extended as an open investigation of long-term treatment.[202] Thirty-seven children who had responded to short-term therapy were offered additional therapy for a total of 1 year. After 14 patients withdrew in the first 3 months, 10 due to lack of efficacy, 18 patients demonstrated at least 90% reduction in AD symptom severity score. Liver function abnormalities were noted in 2 children; this resolved with cessation of treatment. A similar study of 17 adult patients reported fewer patients in complete remission of disease, but tapered dosage had been achieved in all but 2 patients.[203]

A study comparing the herbal decoction used in earlier studies with freeze-dried granules made from the decoction reported significant improvement in erythema and surface damage scores in 18 adult patients, with no differences between treatment groups.[204] The original brewed herb preparation, a commercial product, was compared to placebo in a group of 40 adult and pediatric patients in a double-blind crossover trial that found a general trend toward improvement in both treated and control group patients, with no significant difference for the herbal preparation.[205]

Evidence from the reviewed studies is summarized in the following table.

Table 9.–Summary of Studies of Chinese Herbs in the Treatment of Atopic Dermatitis

Key: AD, atopic dermatitis; dx, diagnosis; f/u, follow-up; grp(s), group(s); pt(s), patient(s); RCT, randomized controlled trial; tx(s), treatment(s) or therapy(ies)

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/Limitations
I	**Sheehan et al., 1992** [200] RCT to evaluate the efficacy and safety of Chinese herbal tx in the tx of AD	40 adult pts with severe refractory AD were randomized to receive 1 of the following for 2 mos, then crossed over to receive the opposite tx: Water-brewed extract of active Chinese herbs (n=20) Water-brewed extract of placebo herbs (n=20) 31 pts completed the study Pts were evaluated at baseline and every 4 wks	Extent and severity of AD assessed by blinded investigators using standardized scoring system for each of 20 body areas on a 0-3 scale Pts reported compliance, itch, sleep, and asthma scores	Pts in both grps showed significant reduction in erythema and extent of skin involvement during tx phase compared with placebo phase 20/31 pts who completed study preferred results of tx phase No significant adverse effects occurred	Validated diagnostic and severity criteria used for enrollment of pts. Standard formula of active herbs written with a Chinese medical practitioner was dispensed to all pts. Placebo herbs similar in odor and taste were dispensed by blinded investigators. Regular dermatological tx was continued by all pts during study. *Limitations:* Relatively small sample, 22% dropout rate
I	**Sheehan and Atherton, 1992**[201] RCT to evaluate the efficacy and safety of Chinese herbal tx in the tx of AD	47 pediatric pts with moderate-to-severe AD were randomized to receive 1 of the following for 2 mos, then crossed over to receive the opposite tx after a 4-wk washout period: Water-brewed extract of active Chinese herbs Water-brewed extract of placebo herbs 37 pts completed the study, and results of both tx sequences were combined Pts were evaluated at baseline and every 4 wks	Extent and severity of AD assessed by blinded investigators using standardized scoring system for each of 20 body areas on a 0-3 scale Parents reported preference for tx or placebo, assessment of sleep	Significant reduction in erythema and extent of skin involvement was noted during tx phase compared with placebo phase No significant adverse effects were reported	Standard formula of active herbs dispensed to all pts. Placebo herbs similar in odor and taste were dispensed by blinded investigators. Pts were instructed to use no topical corticosteroids prior to and during study. *Limitations:* Diagnostic and severity criteria used for enrollment of pts not described. Relatively small sample; 21% dropout rate.

Level of Evidence	Author(s)/Date/ Study Design	Study Population/Intervention	Method of Assessment	Results	Comments/Limitations
III	**Sheehan and Atherton, 1994[202]** Open study to assess safety and efficacy of Chinese herbal tx in the tx of AD	37 pediatric pts (mean age 9.1 yrs) with moderate-to-severe AD who had responded to Chinese herbal tx in earlier trial received water-brewed extract of active Chinese herbs daily Total tx period: daily for 1 yr or until 90% symptom reduction achieved, then frequency reduced 23 pts completed the study Pts were evaluated every 3 mos	Extent and severity of AD assessed using standardized scoring system for each of 20 body areas on a 0-3 scale	18/23 (78%) pts experienced ≥90% reduction of symptoms, with 7 in remission and no longer receiving tx Mean emollient use declined from 60 g/day to 15 g/day Transiently elevated aspartate aminotransferase was noted in 2 children in whom tx was discontinued	Standard formula of active herbs dispensed to all pts. Placebo herbs similar in odor and taste were dispensed by blinded investigators. Length and frequency of tx adjusted individually during study. All pts continued topical 1% hydrocortisone ointment and oral antihistamines at bedtime. *Limitations:* Diagnostic and severity criteria used for enrollment of pts not described. Relatively small sample, 38% dropout rate. Method of quantification of other txs not described.
I	**Fung et al., 1999[205]** RCT to evaluate the effect of Chinese herbal tx in the tx of AD	40 adult and pediatric pts with moderate-to-severe AD were randomized to receive 1 of the following for 2 mos, then crossed over to receive the opposite tx after a 4-wk washout period: Water-brewed extract of active Chinese herbs (n=20) Water-brewed extract of placebo herbs (n=20) 37 pts completed the study Pts were assessed at baseline and every 4 wks	Severity was assessed based on 4 clinical parameters and body areas	No differences were seen between tx and control grp pts. There was a general trend toward improvement in all pts. Approximately equal numbers of pts preferred each tx.	Standard formula of active herbs written with a Chinese medical practitioner was dispensed to all pts. Placebo herbs similar in odor and taste were dispensed by blinded investigators. Valid dx and severity criteria used for enrollment of pts *Limitations:* Relatively small study sample

Homeopathy
No randomized clinical trials of homeopathy in the treatment of AD were identified in the peer-reviewed literature.

Hypnotherapy/biofeedback
Very few clinical investigations of hypnotherapy or biofeedback in the treatment of AD have been published in the peer-reviewed medical literature. McMenamy et al. (1988) described the use of electromagnetic (EMG) biofeedback relaxation training as beneficial for 5 subjects in an open study who received 5 hours of training.[210] Another open study of 18 adult patients in 1995 did not clearly delineate diagnosis criteria, offering therapy to patients for whom dermatological treatment had failed.[211] After 3 to 4 hypnotherapy sessions emphasizing relaxation and mastery were provided, significant reduction of severity was seen in 16 of 18 patients, who also reported improvement in nondermatologic quality-of-life measures.

Massage therapy
One randomized controlled trial of massage in the treatment of AD was available for review.[212] A group of 20 children were randomized to receive either 20 minutes of massage daily from a parent caregiver or standard topical care for 1 month. Clinical severity improved significantly in the treated group, as did quality-of-life measures for the families.

Summary

There is conflicting evidence regarding the efficacy and concerns regarding the toxicity of Chinese herbal therapy for AD. Several small randomized placebo-controlled studies and open trials have suggested that this therapy may reduce symptom severity for some patients, although one randomized placebo-controlled trial of similar size failed to detect a significant treatment effect.

Peer-reviewed clinical studies of the value of homeopathy in the treatment of AD have not been reported. To date, there is no evidence in the literature to support its use in the treatment of AD.

More clinical research is needed to adequately assess the role of hypnotherapy and biofeedback therapy in the treatment of AD, although preliminary results are encouraging.

More clinical research is needed to adequately assess the role of massage therapy in the treatment of AD, although preliminary results are encouraging.

Appendix 1
Expert Work Group and 2nd Expert Reviewers

Atopic Dermatitis Work Group

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