

This report reflects the best available data at the time the report was prepared, but caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations set forth in this report.

Guidelines of care for atopic dermatitis

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DISCLAIMER

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore these guidelines should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient.

INTRODUCTION/METHODOLOGY*

A work group of recognized experts was convened to determine the audience for the guideline, define the scope of the guideline, and identify nine clinical questions to structure the primary issues in diagnosis and management. Work group members were asked to complete a disclosure of commercial supports and this information is in the technical report.

They employed an evidence-based model and the evidence was obtained primarily from a search of MEDLINE and EMBASE databases spanning the

years 1990 to June 3, 2003. Additional searches were done by hand searching publications, including reviews, meta analysis and correspondence. Only English-language publications were reviewed. Statistical assistance was provided by Hayes, Inc, a health technology assistance assessment service. Also, there was reliance on the comprehensive "Systematic Review of Treatments for Atopic Eczema" published as a Health Technology Assessment 2000 and listed in the bibliography.¹

The available evidence was evaluated using a method described by Goodman (1998). Evidence was graded on a five-point scale based on the quality of methodology. 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.

Individual tables are included in the technical report but are also integrated into some of the discussions to illustrate recommendations. Every attempt was made to present a balanced approach to clinical recommendations; however, high-quality randomized clinical trials were often found lacking

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A full technical report that provides a complete description of the methodology is available at our Web site, www.aad.org, or by request at the reprint request address.

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Table I. Prevention measures during pregnancy and after birth

Recommendation	Consensus of opinion	Level of evidence	References
Role of dietary intervention	Unanimous expert opinion	I-II-2	8, 9, 10, 11, 13
Role of aeroallergen avoidance for the mother	Unanimous expert opinion	I	11, 13
Role of prolonged breast feeding	Unanimous expert opinion	II-2	8, 9, 12
Role of probiotics	Unanimous expert opinion	I	14, 15, 16, 17

for the scope of this guideline. In these cases, consensus of expert opinion was used with a grading of available evidence to assist the reader in evaluating the recommendations.

This guideline has been developed in accordance with the American Academy of Dermatology (AAD)/American Academy of Dermatology Association "Administrative Regulations for Evidence-Based Clinical Practice Guidelines" which includes the opportunity for review and comment by the entire AAD membership and final review and approval by the AAD Board of Directors.

SCOPE

This guideline addresses the management of those patients with AD or atopic eczema. Recommendations regarding smallpox vaccinations in AD patients were not addressed in this guideline. These issues are discussed at the following Web sites from the American Academy of Dermatology, American Academy of Dermatology Association, Centers for Disease Control and Prevention, and the Institute of Medicine: www.aad.org, www.aadassociation.org, www.bt.cdc.gov/agent/smallpox, and www4.nationalacademies.org/iom/iomhome.nsf.

DEFINITIONS

Atopic dermatitis (AD) is a chronic inflammatory pruritic skin disease which occurs most frequently in children but can occur in adults and follows a relapsing course. It is often associated with elevated serum IgE levels and a personal or family history of type I allergies, allergic rhinitis, and asthma.²⁻⁷

Atopic eczema is synonymous with AD.

ISSUES

The task force identified the following clinical questions in the management of AD prevention measures during pregnancy and after birth, use of topical corticosteroids, use of other topicals in established dermatitis, use of antihistamines, dietary restrictions, non-pharmacological interventions, systemic immunomodulatory agents and complementary/alternative therapies.

I. Prevention measures during pregnancy and after birth

Recommendations (Table I)

- During pregnancy, there can be no global recommendations regarding dietary interventions and aeroallergen avoidance for the mother; there is no conclusive evidence that manipulation prevents AD either in the infant or child.
- Despite numerous studies, there has been no definitive evidence that exclusive breast-feeding, aeroallergen avoidance, and/or early introduction of solid foods influences the development of AD. There is suggestive evidence that prolonged breast feeding may delay the onset of AD.
- Probiotic treatment during pregnancy and nursing may delay the onset of AD in infants and children.¹⁴⁻¹⁷

Discussion

There is a paucity of well-controlled research that examines the effect of diet, aeroallergen avoidance, and the introduction of solid feeding on the prevention and later onset of AD. The value of exclusive breast-feeding and exclusive diets remains elusive. More studies 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 AD.⁸⁻¹⁷

II. Topical corticosteroids

Recommendations (Table II)

- Topical corticosteroids are the standard of care to which other treatments are compared.
- Cutaneous complications such as striae, atrophy, and telangiectasia limit the long-term use of these agents.
- Despite the extensive use of topical corticosteroids, there are limited data regarding optimal corticosteroid concentrations, duration and frequency of therapy, and quantity of application; similarly, data supporting the perception that long-term corticosteroid use is not associated with extracutaneous adverse effects are lacking.

Table II. Topical corticosteroids

Recommendation	Consensus of opinion	Level of evidence	References
Use of topical corticosteroids	Unanimous expert opinion	II-1 & III	35, 55
Possible cutaneous complications	Unanimous expert opinion	I & III	20, 21 (Appendix 3), 56
Duration of therapy, frequency of application & quantity of application uncertain	Unanimous expert opinion	I-III	18, 19, 36
Effects of hydration/occlusion	Unanimous expert opinion	I & III	19, 37, 43, 44
Possible development of tachyphylaxis	Unanimous expert opinion	No studies	No studies
Role of long-term intermittent application of corticosteroids	Unanimous expert opinion	I	19, 38, 45

- Altering the local environment by hydration and/or occlusion as well as varying the vehicle can impact the absorption and effect of the topical corticosteroid administered.
- Tachyphylaxis is a clinical concern, but there is no experimental documentation.
- The use of long-term intermittent application of corticosteroids appears helpful and safe in two randomized controlled studies.^{19,45} Independent studies of other formulations are needed.

Discussion

Topical corticosteroids, first introduced in the early 1950s have been the mainstay of therapy for atopic dermatitis for many years.^{21,35} This class of drugs is generally the standard to which other therapies are compared. Several fields of medicine (eg, dermatology, allergy, ophthalmology, and otolaryngology) have employed topical corticosteroids therapeutically with what appears to be acceptable effectiveness and safety. Generally, dosing outside of pharmaceutical manufacturers' recommendations cannot be recommended due to lack of data. It is the opinion of the expert work group, that less frequent application (eg, for moderately severe AD of the flexural folds) or more frequent application (eg, for AD of the hands where required frequent hand washing may prohibit optimal absorption) may occasionally be used without a significant resultant alteration in the manufacturers reported efficacy and safety.^{19,21,38,43,44} In one large systematic review, it was found that using twice-daily applications was no more effective than once-daily application.²¹ The approach of using short bursts of potent steroids compared to longer term use of weaker corticosteroids demonstrated no differences in children with mild to moderate AD.³⁸ Steroids in peanut oil vehicles appear to be safe for patients sensitive to peanuts.⁴⁰⁻⁴² Physician and health care provider instructions on application techniques are an important

part in patient education. The lack of information about the amount of medications that are truly used by patients limits our knowledge of the efficacy of these agents; we encourage more precision in dosing in the treatment of AD, establishment of the optimal dose and frequency of application, and the investigation of established and novel vehicles for drug efficacy and safety.^{19,56-59} At this time, long-term intermittent topical steroid application appears helpful and safe in two randomized controlled studies.^{19,45}

Finally, issues regarding potential non-cutaneous side effects still need further study. These include the need for investigation of whether chronic topical corticosteroid application may reduce the linear growth rate in children and bone density in adults.^{22,23,46,47,57,58,60-63} Until such studies have been performed, based on unanimous expert opinion, the following should be considered: the assessment of background risk factors for suboptimal linear growth in children, and for reduced bone density in both children and adults. Also, we believe that treating physicians should remind patients to ingest adequate daily calcium and vitamin D.^{47,60-65}

The potential for topical corticosteroid therapy to suppress the hypothalamic-pituitary-adrenal axis (HPA) in pediatric patients has been investigated in a small number of studies, with inconclusive findings.⁴⁹⁻⁵² Effects on the HPA seem to be associated with percutaneous absorption in patients with more severe disease and those less than 2 years of age.^{37,53-55}

Additionally, there is a theoretical concern regarding topical corticosteroid application to the eyelids with possible increased risk of cataract formation and elevated intraocular pressure cited to occur independent of other factors. While further studies are needed, surveillance ophthalmic examinations should be considered.^{24,48,54}

Table III. Other topical therapies

Recommendations	Consensus of opinion	Level of evidence	References
Use of emollients	Unanimous expert opinion	I	70
Use of pimecrolimus	Unanimous expert opinion	I	89-92
Use of tacrolimus	Unanimous expert opinion	I	73-75, 81, 82
Use of tar	Unanimous expert opinion	II-2	68
Short-term use of doxepin	Unanimous expert opinion	I	67, 68

III. Other topical therapies

Recommendations (Table III)

- Emollients are a standard of care, steroid-sparing, and useful for both prevention and maintenance therapy.
- Calcineurin inhibitors, pimecrolimus, and tacrolimus have been shown to reduce the extent, severity, and symptoms of AD in adults and children.
- Tar may be associated with therapeutic benefits, but is limited by compliance.
- Short-term adjunctive use of topical doxepin may aid in the reduction of pruritus, but the development of side effects may limit usefulness.

Discussion

Emollients. While the use of emollients is considered standard therapy for the treatment of AD, few investigators have studied the effects of emollients alone on the severity of AD symptoms. Three clinical trials were reviewed and these demonstrated enhanced therapeutic response.^{35,70,71}

Calcineurin inhibitors. Both tacrolimus and pimecrolimus are members of this class. There are numerous studies that demonstrate the utility of these agents in AD. The long-term (>1 year) safety, including concerns about immunosuppression and malignancy, remain unanswered.^{72-83,87,89-92}

Tacrolimus (FK-506/Protopic). There is evidence that tacrolimus (FK-506/Protopic) can be effective in reducing the severity of moderate to severe AD in both children over 2 years and adults, with few side effects reported after up to 3 years of treatment.⁷³⁻⁸³ Dropout rates in some of these studies were high, but were generally highest in control groups who experienced little or no improvement. No dose-related response was demonstrated. A burning sensation at the site of application was reported in a number of studies and some adults reported flushing with alcohol ingestion.⁷⁶ Reitamo et al^{81,82} compared two concentrations of tacrolimus ointment (0.03% & 0.1%) to a corticosteroid in two large, multicenter, randomized controlled trials in pediatric and adult populations. In children, both concentrations of tacrolimus ointment appeared more effective than 1% hydrocortisone acetate, with

the higher concentration associated with the greatest reduction in severity.⁸¹ In adults, similar improvement was noted in the midpotency corticosteroid (0.1% hydrocortisone-17-butyrate ointment) and 0.1% tacrolimus ointment groups, and lesser benefit in a group using 0.03% tacrolimus ointment.⁸²

Pimecrolimus (ASM 981/Elidel). There is evidence that therapy with ascomycin (ASM 981/Elidel/pimecrolimus) is safe and effective in reducing the severity of symptoms in children and adults with mild and moderate AD in studies up to 1 year's duration. Reports of randomized clinical trials of ascomycin demonstrated efficacy in reducing symptoms with low systemic absorption.⁸⁴⁻⁸⁸

Coal tar. Although crude coal tar and preparations including coal tar derivatives have been used for many years in the treatment of AD, 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.⁶⁶

Doxepin. There is limited evidence that the use of topical doxepin as short-term adjunctive therapy may provide slight relief of pruritus of limited duration. Sedation and contact allergies may complicate use, and therefore, it is the expert opinion that it should be used for a limited duration.^{67,68}

Phosphodiesterase inhibitors. Topical therapy with phosphodiesterase inhibitors may be valuable in controlling the symptoms of AD; a recent study suggests efficacy comparable to hydrocortisone cream.^{69,93}

IV. Antibiotics and antiseptics

Recommendations (Table IV)

- Patients with AD are commonly colonized with *Staphylococcus aureus*.
- Antibiotics, both systemic and topical, temporarily reduce *S aureus* colonization on the skin.
- Without signs of infection, oral antibiotics generally have a minimal therapeutic effect on the dermatitis. Oral antibiotics can be highly beneficial when skin infection is present.

Table IV. Antibiotics and antiseptics

Recommendation	Consensus of opinion	Level of evidence	References
Staph colonization of the skin	Unanimous expert opinion	I	95
Role of systemic antibiotics	Unanimous expert opinion	I	96
Role of topical antibiotics	Unanimous expert opinion	I	35

Table V. Oral antihistamines

Recommendation	Consensus of opinion	Level of evidence	References
Role of sedative antihistamines	Unanimous expert opinion	I	107, 108
Role of nonsedating antihistamines	Unanimous expert opinion	I	107, 108

- Topical antibiotics can be effective when infection is present; however, development of resistance is a concern.

Discussion

Among adults, children, and infants with AD, many are colonized with *S aureus* in both their affected and unaffected skin.⁹⁴⁻⁹⁷ Although significant reduction of bacterial colonization in the affected and unaffected skin of AD patients by oral antibiotics has been demonstrated, there is little evidence of clinical improvement in the severity of the dermatitis.^{94,98} Ewing et al⁹⁴ (1998) monitored compliance closely and documented temporary reduction of colonizing organisms, but demonstrated no clinical improvement associated with oral antibiotic use. Boguniewicz et al⁹⁸ (2001) demonstrated similar results. Although there are some studies about mupirocin that demonstrate effectiveness, the study design, as well as the development of resistant strains, limits efficacy of this intervention.¹⁰² Oral antibiotics, however, can be highly beneficial when infection is present. Concerns about both oral and topical antibiotics include the possible development of resistance.

Studies of antiseptics showed limited effectiveness in the treatment of AD. Three studies of antiseptics or topical antibacterial agents revealed conflicting evidence to indicate their efficacy in children.^{35,100,101} Stalder et al¹⁰⁰ (1992) reported no difference between treatment of 20 children with chlorohexidine and KMnO₄, and attributed the improvement in both groups to continued use of topical corticosteroids. Ainley-Walker, Patel, and David³⁵ (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. Breneman et al¹⁰¹ (2000) reported significant improvement in patients bathing with triclocarban antibacterial soap.

Combination topical antibiotic (eg, fusidic acid) and topical steroid products have shown efficacy in one study,¹⁰³ while in others, they were no more effective than topical steroid alone.²¹

V. Oral antihistamines

Recommendations (Table V)

- There is little evidence that sedating or nonsedating antihistamines are effective in relieving itch or urticarial symptoms associated with AD.
- For patients with significant sleep disruption due to itch, allergic dermatographism, or allergic rhinoconjunctivitis, sedating antihistamines may be useful. Many patients with AD also have accompanying allergic rhinoconjunctivitis, urticaria, and dermatographism and therefore may be benefited by the use of antihistamines.

Discussion

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 or soporific 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.¹⁰⁴⁻¹¹¹

In an evidence-based review of the literature from 1966 to 1999, Klein and Clark¹⁰⁴ remarked on the paucity of proper clinical trials and concluded that there is no evidence to support the efficacy of non-sedating antihistamines in AD. Antihistamines are safe and not associated with significant adverse effects, even in very young patients.¹⁰⁶⁻¹¹¹ Many patients with AD also have accompanying urticaria, dermatographism, and allergic rhinoconjunctivitis, and therefore they may be benefited by the use of antihistamines for these concurrent medical problems.

Table VI. Dietary restrictions in established atopic dermatitis

Recommendation	Consensus of opinion	Level of evidence	References
Role of dietary egg restriction	Unanimous opinion	I-III	112,113,114
Role of vitamin and mineral supplements, and evening primrose oil	Unanimous opinion	I	118, 119, 120, 121

Table VII. Nonpharmacological interventions

Recommendation	Consensus of opinion	Level of evidence	References
Role of psychotherapeutic approaches	Unanimous opinion	III	137, 138, 139
Role of broad-band UVB & UVA	Unanimous opinion	I	151
Role of narrow-band UVB	Unanimous opinion	I-III	141, 142, 146, 147, 151
Role of PUVA	Unanimous opinion	II-2-III	140-142,145
Role of UVA1	Unanimous opinion	I	148
Role of house dust mite allergen reduction	Unanimous opinion	I	126, 128, 131

PUVA, Psoralen plus ultraviolet A; UVA, ultraviolet A; UVB, ultraviolet B.

VI. Dietary restrictions in established AD

Recommendations (Table VI)

- Dietary restriction of eggs may be beneficial in infants with IgE reactivity to egg, but there is no evidence that other restrictions in diet are of therapeutic value for established AD.
- There is no evidence that fish oil, borage oil, evening primrose oil, or vitamin or mineral supplements have therapeutic value in AD.
- Immediate-type hypersensitivity reactions such as urticaria are common in this population and may be mistaken for AD.

Discussion

Dietary restriction. Several randomized controlled trials and descriptive studies evaluating the effect of dietary restriction on AD were identified in the literature search. There was no consistent finding regarding the role of dietary restriction in young children with AD.¹¹²⁻¹¹⁴ There is some evidence that avoidance of foods to which there is a known sensitivity may reduce the severity and extent of AD, but causality is difficult to establish when this is tested. High dropout rates are often present in these studies because of the difficulties of a highly restrictive diet to patients and their parents. A randomized controlled trial by Lever et al (1998) found that an egg-free diet was associated with an improvement in severity of AD in infants with a positive RAST to eggs, with the greatest effect in those most severely affected.¹¹³ A separate study of this highly restricted diet found it to be nutritionally inadequate.¹¹⁵

Evidence regarding the role of exclusive breast-feeding suggests that this has little protective or

therapeutic effect. A descriptive study by Isolauri et al¹¹⁶ 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 in whom this was not effective, cessation of breast-feeding was associated with improvement in AD.^{17,116}

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 and while some suggested efficacy, the majority suggested no efficacy.¹¹⁸⁻¹²² Another study demonstrated no clinical effect of utilizing borage oil, compared with bland lipid placebo, for patients with AD.¹²¹

Pyridoxine, vitamin E and multivitamins, and zinc supplementation. There is no evidence that pyridoxine, vitamin E, multivitamins, and zinc supplementation reduce the extent and severity of AD.^{123,124}

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 *Lactobacillus* preparations commercially available in the United States would achieve the same results.

VII. Non-pharmacological interventions

Recommendations

- Psychotherapeutic approaches to the treatment of AD (Table VII) are supported for a combina-

tion of educational and psychological interventions.

- Ultraviolet (UV) phototherapy, including combination broad-band ultraviolet B (UVB)/ultraviolet A (UVA), narrowband UVB therapy, psoralen plus ultraviolet A (PUVA), and UVA1 is well established in the treatment of AD, although relapse following cessation of therapy frequently occurs.
- It is unclear if house dust mite strategies are effective for most patients with AD.

Discussion

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. The use of topical corticosteroids decreased significantly, and in one study this effect persisted for up to 2 years.^{137,138} 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

Nurse education. Nursing education is associated with enhanced patient compliance, an increase in the appropriate use of prescribed topical corticosteroid therapy, and significant clinical improvement in the clinical condition.^{134,135}

UV phototherapy. A relatively large number of reports on the effect of UV phototherapy, including studies of photochemotherapy using methoxypsoralen (PUVA therapy) were identified in the peer-reviewed literature, although only a few were randomized controlled clinical trials. Most patients in these studies experienced substantial improvement in symptoms, and use of topical corticosteroid was significantly reduced.¹⁴³ Several studies involving PUVA combined with topical corticosteroids demonstrated substantial improvement.^{140-142,145}

Broadband UVB and UVA/B have been used for the treatment of AD. In a paired comparison study by Jekler and Larkö¹⁴⁰ UVA/B was significantly better than broadband UVB alone.

The role of narrowband UVB (wavelength 310-315 nm) in the treatment of AD has recently been elucidated.^{141,142,146,147,151} The potential combination of this modality with UVA may offer advantages, but this has not been evaluated.

Krutmann et al¹⁴⁸ evaluated the efficacy of high-dose UVA1 therapy (wavelength 340-400 nm) for patients with severe AD. High-dose UVA1 was associated with significantly greater improvement in severity scoring compared to corticosteroid, and both

UVA1 phototherapy and corticosteroid therapy alone were superior to UVA/B therapy.

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.^{153,154}

House dust mite reduction. Several studies of the effect of house dust mite reduction were identified in the peer-reviewed literature with conflicting results.¹²⁵⁻¹³⁰ Two reports 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 and prolonged remission for patients with high house dust mite-specific immunoglobulin E (IgE) levels treated in such "clean" rooms.^{126,127} 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 There were conflicting studies on mattress covers and bedding among adult patients.^{126,129} Patients who have concurrent asthma and/or rhinoconjunctivitis may benefit from dust mite reduction, but there is no intervention effective for most patients with AD.

Avoidance of enzyme-enriched detergents. 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. However, in patients with known hypersensitivity to enzyme proteins, enriched detergents should be avoided.

Specialized clothing. There are no clinical trials investigating the value of avoiding wool and harsh clothing in the treatment of AD. However, based on expert opinion, it is recommended that patients be advised to choose more comfortable fabrics such as cotton.

Balneotherapy. No clinical trials of the efficacy of salt baths were identified in the peer-reviewed literature, and the duration of effect and the generalizability of one study are uncertain.¹³³

VIII. Systemic immunomodulatory agents

Recommendations (Table VIII)

- Cyclosporine is effective in the treatment of severe AD, but its usefulness may be limited by side effects.
- Interferon gamma may be effective, but the evidence is limited in a subset of patients.
- Systemic corticosteroids are known to be effective in the short-term treatment of AD, but no evidence

Table VIII. Systemic immunomodulatory agents

Recommendation	Consensus of opinion	Level of evidence	References
Role of cyclosporine	Unanimous opinion	I	168
Role of recombinant human interferon gamma	Unanimous opinion	I	180, 184, 186
Role of systemic corticosteroids	Unanimous opinion	III	155
Role of mycophenolate mofetil, IVIg, and azathioprine	Unanimous opinion	II-2-III	190-195

IVIg, Intravenous immunoglobulin.

exists to support their use, and rebound flaring and long-term side effects are limiting.

Conflicting data exist about the efficacy of azathioprine, mycophenolate mofetil, and intravenous immunoglobulin (IVIg).

There is insufficient evidence to support the role of leukotriene inhibitors, thymopentin (TP-5), allergen-antibody complexes of house dust mites, desensitization injections, theophylline, and papaverine in the treatment of AD.

Discussion

Systemic immunomodulatory agents have been studied in recent years generally as therapy for refractory AD that does not respond to topical therapies.¹⁵⁵ Some systemic immunomodulatory agents, such as cyclosporine, have been extensively studied in randomized controlled trials. Systemic corticosteroids (including oral and intramuscular), although commonly used in the treatment of refractory AD and known to be effective, have not been systematically evaluated for dosing or safety in this indication. The risk of systemic toxicity and frequent incidence of rebound flare limit the usefulness of these modalities. Interferon gamma has been investigated in only a small number of studies; there is early evidence for its efficacy.^{180-184,186}

Studies of medications including azathioprine, mycophenolate mofetil, and IVIg have produced conflicting results to make definitive conclusions about their role in the therapeutic armamentarium of atopic dermatitis.¹⁹⁰⁻¹⁹⁵

Cyclosporine. Trials with cyclosporine demonstrated prompt relief of symptoms with rapid relapse after cessation of treatment.¹⁶⁵ Long-term maintenance therapy affords patients satisfactory maintenance of remissions.¹⁶⁶⁻¹⁷⁹

The effect of a short-course cyclosporine therapy (12-week cycles with at least 7 days between each course of therapy) versus continuous therapy (therapy for 1 year) in a group of children, resulted in significantly lower cumulative total dose of the medication compared to those requiring continuous therapy.¹⁷⁸

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, 3 randomized, controlled clinical trials were available for review and analysis.^{180,184,186} Interferon gamma has been reported to provide significant relief of AD symptoms, although there is a demonstrated high overall rate of side effects.¹⁸⁰⁻¹⁸⁴

Systemic corticosteroids. Occasional short-term oral therapy with prednisone or intramuscular injections of triamcinolone acetonide are 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 despite its long-standing role in the treatment of AD.

Azathioprine. A recent randomized, double-blind, placebo-controlled trial examined the use of azathioprine 2.5 mg/kg per day in the treatment of AD but conclusions were limited by a high dropout rate.¹⁹² Similarly, Berth-Jones et al¹⁹³ demonstrated azathioprine effectiveness, but potential toxicities limited the usefulness of this agent.

Mycophenolate mofetil. Two small open reports that investigated the efficacy of mycophenolate mofetil suggested possible benefit in the treatment of AD.^{194,195}

Intravenous immunoglobulin. There have been a few open clinical studies of the use of IVIg for the treatment of AD, and results have been mixed.^{190,191}

Leukotriene inhibitors, methotrexate, desensitization injections, theophylline and papaverine, thymopentin, tumor necrosis factor inhibitors, oral pimecrolimus, allergen-antibody complexes of house dust mites. There is insufficient evidence in the peer-reviewed literature to support the use of leukotriene inhibitors, desensitization injections, allergy-antibody complexes of house dust mites, thymopentin, theophylline, and papaverine

Table IX. Complementary/alternative therapies

Recommendation	Consensus of opinion	Level of evidence	References
Role of Chinese herbal therapy	Unanimous opinion	I	200, 201, 205

for the treatment of AD.^{157-164,187-189,196-198} Although of interest, clinical trials regarding the possible use of methotrexate, biologic agents such as etanercept, infliximab, and oral pimecrolimus in the treatment of AD are not currently available. Therefore, these agents are outside the scope of this report.

IX. Complementary/alternative therapies Recommendations

- There is conflicting evidence regarding efficacy (Table IX) and potential concerns regarding hepatic and other toxicities of Chinese herbal therapy for AD.
- 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, acupuncture, massage therapy, and biofeedback therapy in the treatment of AD, although preliminary results are encouraging.

Discussion

Chinese herbs. 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.¹⁹⁹⁻²⁰⁹

Homeopathy. 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.

Hypnotherapy/biofeedback. More clinical research is needed to adequately assess the role of hypnotherapy, biofeedback therapy, and massage therapy in the treatment of AD, although preliminary results are encouraging.^{210,211}

Massage therapy. One small study yielded positive findings in the use of massage therapy as a replacement for standard topical care with a reduction in clinical symptoms of AD.²¹²

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