Guidelines of care for the management of atopic dermatitis

Section 3. Management and treatment with phototherapy and systemic agents

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

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

Atopic dermatitis is a chronic, pruritic inflammatory dermatosis that affects up to 25% of children and 2% to 3% of adults. This guideline addresses important clinical questions that arise in atopic dermatitis management and care, providing recommendations based on the available evidence. In this third of 4 sections, treatment of atopic dermatitis with phototherapy and systemic immunomodulators, antimicrobials, and antihistamines is reviewed, including indications for use and the risk-benefit profile of each treatment option. (J Am Acad Dermatol 2014;71:327-49.)

Key words: atopic dermatitis; azathioprine; cyclosporin A; interferon gamma; methotrexate; mycophenolate mofetil; oral antihistamines; oral antimicrobials; oral steroids; photochemotherapy; phototherapy; systemic therapy.

DISCLAIMER

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be interpreted as setting a standard of care, or be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient, and the known variability and biological behavior of the disease. This guideline reflects the best available data at the time the guideline was prepared. The results of future studies may require

From the Department of Dermatology, Seattle Children's Hospital[a]; Department of Dermatology, Mayo Clinic, Rochester[b]; Department of Dermatology, New York University School of Medicine[c]; Department of Dermatology, University of California, San Francisco[d]; Department of Dermatology and Skin Science, University of British Columbia[e]; Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago[f]; Department of Dermatology, Case Western University, Cleveland[g]; Department of Dermatology, Wake Forest University Health Sciences, Winston-Salem[h]; Department of Dermatology, Oregon Health and Science University[i]; Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine[j]; Kaplan-Amonette Department of Dermatology, University of Tennessee Health Science Center[k]; private practice, Fairfax[l]; University of San Diego[m]; Division of Pediatric and Adolescent Dermatology, Rady Children's Hospital, San Diego[n]; Center of Evidence-based Dermatology, Nottingham University Hospitals National Health Service Trust[o]; Department of Dermatology, University of Alabama at Birmingham[p]; National Eczema Association, San Rafael[q]; and American Academy of Dermatology, Schaumburg.[r]

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Reprint requests: Wendy Smith Begolka, MBS, American Academy of Dermatology, 930 E Woodfield Rd, Schaumburg, IL 60173. E-mail: wsmithbegolka@aad.org.

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Abbreviations used:

AAD:	American Academy of Dermatology
AD:	atopic dermatitis
AZA:	azathioprine
BB:	broadband
CSA:	cyclosporin A
FDA:	Food and Drug Administration
GI:	gastrointestinal
HSV:	herpes simplex virus
IFN-G:	interferon gamma
MMF:	mycophenolate mofetil
MTX:	methotrexate
NB:	narrowband
PUVA:	psoralen plus ultraviolet A
QOL:	quality of life
SASSAD:	Six Sign Six Area Atopic Dermatitis
SCORAD:	SCORing Atopic Dermatitis
TPMT:	thiopurine methyltransferase
UV:	ultraviolet

revisions to the recommendations in this guideline to reflect new data.

SCOPE

This guideline addresses the treatment of pediatric and adult atopic dermatitis (AD; atopic eczema) of all severities, although systemic modalities are mainly recommended for moderate to severe disease, or for patients whose dermatitis causes significant psychosocial impact. The treatment of other forms of eczematous dermatitis is outside the scope of this document. Recommendations on AD treatment and management are subdivided into 4 sections given the significant breadth of the topic, and to update and expand on the clinical information and recommendations previously published in 2004.[1] This document is the third of 4 publications in the series and discusses the management of AD via phototherapy and systemic agents, including immunomodulators, antimicrobials, and antihistamines.

METHOD

A work group of recognized AD experts was convened to determine the audience and scope of the guideline, and to identify important clinical questions in the use of phototherapy and systemic agents for the treatment of AD (Table I). Work group members completed a disclosure of interests that was updated and reviewed for potential relevant conflicts of interest throughout guideline development. If a potential conflict was noted, the work group member recused himself or herself from discussion and drafting of recommendations pertinent to the topic area of the disclosed interest.

An evidence-based model was used and evidence was obtained using a search of the PubMed and the Global Resources for Eczema Trials[2] databases from November 2003 through November 2012 for clinical questions addressed in the previous version of this guideline published in 2004, and 1960 through 2012 for all newly identified clinical questions as determined by the work group to be of importance to clinical care. Searches were prospectively limited to publications in the English language. Medical Subject Headings terms used in various combinations in the literature search included: "atopic dermatitis," "atopic eczema," "systemic agent(s)," "immunomodulatory," "immunosuppressive," "cyclosporine," "azathioprine," "mycophenolate mofetil," "methotrexate," "interferon gamma," "prednisone," "prednisolone," "biologics," "TNF-alpha inhibitor," "etanercept," "infliximab," "leukotriene inhibitor," "omalizumab," "oral tacrolimus," "oral pimecrolimus," "ascomycin," "thymopentin/TP-5," "intravenous immunoglobulin," "theophylline," "papaverine," "phototherapy," "photochemotherapy," "ultraviolet," "laser," "systemic/oral antimicrobial," "systemic/oral antibiotic," "antihistamines," "cetirizine," "fexofenadine," "loratadine," "terfenadine," "olopatadine," "clemastine," "leukotriene," "zafirlukast," and "montelukast."

A total of 1063 abstracts were initially assessed for possible inclusion. After removal of duplicate data, 185 were retained for final review based on relevancy and the highest level of available evidence for the outlined clinical questions. Evidence tables were generated for these studies and used by the work group in developing recommendations. The American Academy of Dermatology's (AAD's) prior published guidelines on AD were evaluated, as were other current published guidelines on AD.[1,3-5]

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

I. Good-quality *patient-oriented evidence* (ie, evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life [QOL]).
II. Limited-quality patient-oriented evidence.
III. Other evidence including consensus guidelines, opinion, case studies, or *disease-oriented evidence* (ie, evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes).

Table I. Clinical questions used to structure the evidence review for the treatment of atopic dermatitis with phototherapy and systemic agents

- Which immunomodulatory agents are efficacious and safe for the treatment of atopic dermatitis?
  - Cyclosporin A
  - Azathioprine
  - Mycophenolate mofetil
  - Methotrexate
  - Interferon gamma
  - Systemic steroids
  - Tumor necrosis factor-alpha inhibitors (etanercept, infliximab)*
  - Leukotriene inhibitors
  - Omalizumab*
  - Oral calcineurin inhibitors
  - Other (eg, thymopentin (TP)/TP-5, intravenous immunoglobulin, theophylline, papaverine)
- What is the efficacy of systemic antimicrobials and systemic antihistamines for the treatment of atopic dermatitis?
- What is the optimal dose, frequency of use, adverse effects, and efficacy of phototherapy and photochemotherapy for the treatment of atopic dermatitis?

*Indicates new clinical questions.

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

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

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

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

DEFINITION

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

Table II. Recommendations for the use of phototherapy

Phototherapy is a second-line treatment, after failure of first-line treatment (emollients, topical steroids, and topical calcineurin inhibitors).
Phototherapy can be used as maintenance therapy in patients with chronic disease.
Phototherapy treatment of all forms should be under the guidance and ongoing supervision of a physician knowledgeable in phototherapy techniques.
The light modality chosen should be guided by factors such as availability, cost, patient skin type, skin cancer history, and patient use of photosensitizing medications.
The dosing and scheduling of light should be based on minimal erythema dose and/or Fitzpatrick skin type.
Home phototherapy under the direction of a physician may be considered for patients who are unable to receive phototherapy in an office setting.

INTRODUCTION

Despite its relapsing and remitting nature, the majority of patients with AD can achieve clinical improvement and disease control with nonpharmacologic interventions (eg, emollient use), conventional topical therapies (including corticosteroids and calcineurin inhibitors), and environmental and occupational modifications, when necessary. Phototherapy is recommended as a treatment for both acute and chronic AD in children and adults, after failure of the measures mentioned above. Systemic immunomodulatory agents are indicated and recommended for the subset of adult and pediatric patients in whom optimized topical regimens using emollients, topical anti-inflammatory therapies, adjunctive methods, and/or phototherapy do not adequately control the signs and symptoms of disease, and contact dermatitis has been considered. Phototherapy and systemic immunomodulating agents may also be used in patients whose medical, physical, and/or psychological states are greatly affected by their skin disease, which may include negative impact on work, school performance, or interpersonal relationships. Despite their frequent use in clinical practice, oral antihistamines and systemic antimicrobials appear to be of benefit only for specific circumstances (detailed below), based on the scientific data to date.

PHOTOTHERAPY

The use of light waves as a medical therapy began in the 1890s. The most relevant use of

Table III. Strength of recommendations for the management and treatment of atopic dermatitis with phototherapy and systemic agents

Recommendation	Strength of recommendation	Level of evidence	References
Phototherapy (all forms)	B	II	9-16,19,22-26
• Home phototherapy	C	III	27
Cyclosporine	B	I-II	34-43
Azathioprine	B	II	33,44-51
Methotrexate	B	II	33,42,52-56
Mycophenolate mofetil	C	III	34,57,58
Interferon gamma	B	II	59,60
Systemic steroids	B	II	4,35
Systemic antibiotics			
• None, if noninfected AD	B	II	64-67
• For infected AD	A	II	64-67
• Concurrent topical steroid treatment during oral antibiotic course	C	III	No clinical trials
Systemic antivirals for eczema herpeticum	C	II	68
Against use of systemic antihistamines			
• Sedating	C	III	69-73
• Nonsedating	A	II	69-73

AD, Atopic dermatitis.

phototherapy in dermatology today is in the treatment of refractory or extensive psoriasis, first reported by Goeckerman[8] in 1925, with use of broadband (BB) ultraviolet (UV)B in combination with crude coal tar. Decades later, Morison et al[9] noticed patients with refractory AD improved in sunny climates, and thus attempted to treat these patients with oral psoralen and UV light, with success. Their publication is considered a milestone report in the use of phototherapy for AD treatment.

Efficacy

Numerous studies document the efficacy of phototherapy for AD.[10-15] Recommendations for its use in AD management are summarized in Table II, and the strength of recommendation is summarized in Table III. Multiple forms of light therapy are beneficial for disease and symptom control, including: natural sunlight, narrowband (NB) UVB, BB-UVB, UVA, topical and systemic psoralen plus UVA (PUVA), UVA and UVB (UVAB), and Goeckerman[8] therapy. Although it would be helpful to denote 1 or more forms of phototherapy as superior to all, this is not possible given limited head-to-head trials and a lack of comprehensive comparative studies. Most studies involve small sample sizes, and the dosing parameters vary widely. Thus, no definitive recommendation can be made to differentiate between the various forms of phototherapy in regards to efficacy, although natural sunlight is likely less effective than artificial light sources.[10] UVA phototherapy and UVAB phototherapy have increased risks of side effects (as mentioned below), and UVAB is of limited availability. NB-UVB is generally the most commonly recommended light treatment by providers when considering its low risk profile, relative efficacy, availability, and provider comfort level.

Dosage and scheduling

Treatment protocols and parameters for the use of phototherapy in patients with AD are numerous, fluid, and heterogenous. Many providers, because of familiarity and ease of use, initiate therapy based on the phototherapy dosing protocols outlined in the AAD psoriasis guidelines shown in Tables IV-VI.[16] In general, patients are dosed according to their minimal erythema dose and/or Fitzpatrick skin type. Just as with other medical treatments, phototherapy protocols and their adjustments should be structured and reviewed by a medical provider knowledgeable in phototherapy techniques. Dosing protocols differ for BB-UVB and NB-UVB and are not interchangeable, and phototherapy equipment varies between manufacturers. Many pertinent variables will determine which light modality is chosen for a particular patient, including local availability and cost. Providers should also be diligent about the key components of the patient's history and physical examination of relevance to phototherapy, including skin cancer history and the use of prescription and over-the-counter topical and oral products that may be photosensitizing. Phototherapy can be administered on a scheduled but intermittent basis over time, or more continuously as maintenance therapy, for patients with refractory or chronic disease.[15,16]

Table IV. Dosing guidelines for broadband ultraviolet B

According to skin type:		
Skin type	**Initial UVB dose, mJ/cm²**	**UVB increase after each treatment, mJ/cm²**
I	20	5
II	25	10
III	30	15
IV	40	20
V	50	25
VI	60	30

According to MED:	
Initial UVB	50% of MED
Treatments 1-10	Increase by 25% of initial MED
Treatments 11-20	Increase by 10% of initial MED
Treatment ≥21	As ordered by physician

If subsequent treatments are missed for:	
4-7 d	Keep dose same
1-2 wk	Decrease dose by 50%
2-3 wk	Decrease dose by 75%
3-4 wk	Start over

Administered 3-5 times/wk.
MED, Minimal erythema dose; *UV*, ultraviolet.
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Table V. Dosing guidelines for narrowband ultraviolet B

According to skin type:			
Skin type	**Initial UVB dose, mJ/cm²**	**UVB increase after each treatment, mJ/cm²**	**Maximum dose, mJ/cm²**
I	130	15	2000
II	220	25	2000
III	260	40	3000
IV	330	45	3000
V	350	60	5000
VI	400	65	5000

According to MED:	
Initial UVB	50% of MED
Treatments 1-20	Increase by 10% of initial MED
Treatment ≥21	Increase as ordered by physician

If subsequent treatments are missed for:	
4-7 d	Keep dose same
1-2 wk	Decrease dose by 25%
2-3 wk	Decrease dose by 50% or start over
3-4 wk	Start over

Maintenance therapy for NB-UVB after >95% clearance:		
1×/wk	NB-UVB for 4 wk	Keep dose same
1×/2 wk	NB-UVB for 4 wk	Decrease dose by 25%
1×/4 wk	NB-UVB	50% of highest dose

Administered 3-5 times/wk.
Because there is broad range of MED for NB-UVB by skin type, MED testing is generally recommended.
It is critically important to meter UVB machine once weekly. UVB lamps steadily lose power. If UV output is not periodically measured and actual output calibrated into machine, clinician may have false impression that patient can be treated with higher doses when machine is actually delivering much lower dose than number entered.
Minimum frequency of phototherapy sessions required per week for successful maintenance and length of maintenance period varies tremendously between individuals. Above table represents most ideal situation where patient can taper off phototherapy. In reality, many patients require 1×/wk NB-UVB phototherapy indefinitely for successful long-term maintenance.
MED, Minimal erythema dose; *NB*, narrowband; *UV*, ultraviolet.
Reprinted with permission.[16]

Phototherapy can be used as monotherapy or in combination with emollients and topical steroids. The use of phototherapy with topical calcineurin inhibitors is cautioned, as the manufacturers suggest limiting exposure to natural and artificial light sources while using these topical medications.[17,18] The use of light therapy may decrease the need for topical steroid and topical immunomodulator use. Risks and benefits, and pragmatic concerns (eg, cost, availability, patient compliance) should be considered when formulating the optimal treatment course for the patient.

Adverse effects

The true incidence of adverse events with provider-monitored phototherapy is unknown, but considered to be low. Available studies report minimal noncompliance rates secondary to side effects.[10,12-15] Moreover, the majority of publications on phototherapy side effects address treatment of patients with psoriasis. How this relates to outcomes for patients with AD is unclear. Nonetheless, caution and due diligence are warranted as with any other medical therapy given to patients. Different forms of phototherapy have distinct risk profiles that the clinician must take into account.[16,19-21] Several common adverse effects include: actinic damage, local erythema and tenderness, pruritus, burning, and stinging. Less common consequences of light therapy include: nonmelanoma skin cancer, melanoma (particularly with the use of PUVA),[21] lentigines, photosensitive eruptions (especially polymorphous light eruption), folliculitis, photo-onycholysis, herpes simplex virus (HSV) reactivation, and facial hypertrichosis. Cataract formation is a recognized side effect specific to UVA therapy, whereas the addition of oral psoralen to UVA treatment frequently causes patients to have headaches, nausea, and vomiting, and rarely hepatotoxicity. Oral psoralen also increases a patient's photosensitivity, both cutaneous and ocular, for several hours after ingestion.

Table VI. Dosing of UVA radiation for oral psoralen plus ultraviolet A

Skin type	Initial dose, J/cm^2	Increments, J/cm^2	Maximum dose, J/cm^2
I	0.5	0.5	8
II	1.0	0.5	8
III	1.5	1.0	12
IV	2.0	1.0	12
V	2.5	1.5	20
VI	3.0	1.5	20

Reprinted with permission.[16]

Pediatric considerations

Several studies document the safe and effective use of both UVA and UVB phototherapy in children and adolescents.[12,13,15,22-26] Additional psychosocial factors must be anticipated and addressed to successfully treat younger patients, as lamps and machines can appear intimidating, and caregivers often have many questions and concerns. There are no known studies that report the long-term consequences of phototherapy use in children with AD. An increased risk of nonmelanoma skin cancer has been reported in children receiving PUVA treatment for psoriasis.[16] Centered on 311 to 313 nm, NB-UVB is safe and effective for a number of photoresponsive dermatoses in children and is often considered as a first-line agent because of its ease of administration and safety profile relative to PUVA. Thus, phototherapy as a treatment for children with AD unresponsive to multimodal topical measures is appropriate. The wavelength selection and treatment course should be individualized.

Home phototherapy

The greatest barrier to more widespread use of phototherapy is frequent travel to a provider of this therapeutic modality. Home phototherapy would, no doubt, make this an excellent alternative before systemic treatments. However, there are no studies to date that document the efficacy or safety of home light therapy for patients with AD, or that contrast its use to in-office phototherapy. Home UVB treatment is not uncommonly used in the treatment of psoriasis. The PLUTO study by Koek et al[27] demonstrated that patients with psoriasis treated with home NB-UVB phototherapy units experienced decreased burden of treatment and increased satisfaction versus in-office NB-UVB treatment, whereas Psoriasis Area and Severity Index score reduction, cumulative doses, and incidence of short-term side effects (up to 46 irradiations) were not significantly different. Although this study does not generalize to patients with AD, similar results might be expected. Therefore, home phototherapy under the direction of a physician may be considered for patients who are unable to receive phototherapy in an office setting.

Lasers and extracorporeal photochemotherapy

The successful use of UV light for AD has led to the investigation of laser light technology as another possible treatment. Various laser modalities, including excimer, diode, and pulsed dye lasers, have been tested in patients with AD, with some improvement in symptoms such as pruritus and QOL.[28-30] However, given a very limited number and quality of reports, lasers are not recommended for the treatment of AD at this time.

Extracorporeal photochemotherapy has been used in patients with generalized and erythrodermic AD to attempt to control disease severity and symptomatology.[31,32] Response rates differ among patients, ranging from complete remission to no response. Given this lack of consistent improvement, extracorporeal photochemotherapy is not recommended for the routine treatment of AD.

SYSTEMIC AGENTS

Systemic immunomodulating medications are a prevalent treatment option for the management of chronic and/or severe inflammatory diseases. Their use in dermatology is commonplace for blistering disorders, granulomatous diseases, and most frequently, psoriasis. As discussed earlier, these agents are indicated and recommended in AD care for the subset of adult and pediatric patients in whom optimized topical regimens and/or phototherapy do not adequately control the disease, or when QOL is substantially impacted. There are few studies in the literature that compare different systemic therapies with one another in a randomized, controlled fashion.[33-35] Thus, it is difficult to determine the relative efficacy of the available options. Prevailing literature suggests that cyclosporine, methotrexate (MTX), mycophenolate mofetil (MMF), and azathioprine (AZA) are used the most and are more efficacious in treating AD, whereas other agents (leukotriene inhibitors, oral calcineurin inhibitors) have limited data. Biologic drugs are relatively new and the lack of available data prevents a recommendation for use in AD at this time. The management of AD with systemic corticosteroids, although used frequently and shown to temporarily suppress disease, should generally be avoided because of short- and long-term adverse effects and an overall unfavorable risk-benefit profile. Short courses of oral corticosteroids may lead to atopic flares.

Table VII. Recommendations for the use of systemic immunomodulatory agents

Systemic immunomodulatory agents are indicated for the subset of adult and pediatric patients in whom optimized topical regimens and/or phototherapy do not adequately control the signs and symptoms of disease.
Systemic immunomodulatory agents are indicated when the patient's skin disease has significant negative physical, emotional, or social impact.
All immunomodulatory agents should be adjusted to the minimal effective dose once response is attained and sustained. Adjunctive therapies should be continued to use the lowest dose and duration of systemic agent possible.
Insufficient data exist to firmly recommend optimal dosing, duration of therapy, and precise monitoring protocols for any systemic immunomodulating medication.
Treatment decisions should be based on each individual patient's AD status (current and historical), comorbidities, and preferences.
Cyclosporine is effective and recommended as a treatment option for patients with AD refractory to conventional topical treatment.
Azathioprine is recommended as a systemic agent for the treatment of refractory AD.
Methotrexate is recommended as a systemic agent for the treatment of refractory AD. Folate supplementation is recommended during treatment with methotrexate.
Mycophenolate mofetil may be considered as an alternative, variably effective therapy for refractory AD.
Interferon gamma is moderately and variably effective and may be considered as an alternative therapy for refractory AD in adults and children who have not responded to, or have contraindications to the use of, other systemic therapies or phototherapy.
Systemic steroids should be avoided if possible for the treatment of AD. Their use should be exclusively reserved for acute, severe exacerbations and as a short-term bridge therapy to other systemic, steroid-sparing therapy.

AD, Atopic dermatitis.

Recommendations for the use of systemic immunomodulating agents in the management of AD are summarized in Table VII. Dosing and monitoring guidelines for the use of systemic agents are summarized in Table VIII, whereas Table IX summarizes the potential adverse effects, interactions, and contraindications of the systemic immunomodulatory agents.

CYCLOSPORINE

Cyclosporin A (CSA) was discovered in the 1970s as an effective immunosuppressant of T cells and interleukin-2 production. From its original use as a graft antirejection medication in transplant recipients, its expanded therapeutic benefits have been proven in several immune-mediated skin diseases, including graft-versus-host disease and psoriasis.[36] The treatment of refractory AD with CSA was first reported by Allen[37] in 1991.

CSA is an effective off-label treatment option for patients with AD refractory to conventional topical treatment. Further details regarding the administration of CSA can be found in Tables VIII and IX, and the strength of recommendation is summarized in Table III.

Efficacy

CSA is efficacious in treating AD, with most patients noting a significant decrease in disease activity within 2 to 6 weeks of treatment initiation.[36] For example, 1 study randomized 46 patients with severe AD to CSA or placebo therapy.[38] Patients who received CSA had both a decrease in surface area of involvement and in the degree of inflammation of the remaining dermatitis at the 6-week time mark. These patients had a mean decrease in total body severity assessment of 55%, compared with an increase of 4% in patients taking placebo. The mean score for extent of disease, measured by the rule-of-nines area assessment, decreased by 40% in patients taking cyclosporine, compared with an increase of 25% in those taking placebo. The drug was deemed moderately beneficial relative to placebo.

Dosage and scheduling

The dosage of CSA used for AD treatment varies greatly, ranging from 3 to 6 mg/kg/d, standardly 150 to 300 mg/d in adults.[39] Reports suggest that higher initial doses result in more rapid control of the disease and involved body surface area while improving QOL measures, such as pruritus and sleep disturbance.[39] The initial and maintenance dose of CSA prescribed should be based on multiple factors, including the patient's disease severity and other medical morbidities. Although all formulations of CSA are effective in AD, the microemulsion

Table VIII. Dosing and monitoring guidelines for the use of selected systemic agents

Drug	Dosing	Baseline monitoring	Follow-up monitoring	Miscellaneous
Cyclosporine	150-300 mg/d Pediatric: 3-6 mg/kg/d	Blood pressure ×2 measurements Renal function Urinalysis with microscopic analysis Fasting lipid profile CBC/differential/platelets Liver function Mg+ K+ Uric acid TB testing HIV if indicated HCG if indicated	Blood pressure every visit Every 2 wk for 2-3 mo, then monthly: renal function, liver function, lipids, CBC/differential/platelets, Mg+, K+, uric acid If dose increased, check laboratory results 2-4 wk after HCG if indicated Annual TB testing	If Cr increases >25% above baseline, reduce dose by 1 mg/kg/d for 2-4 wk and recheck; stop CSA if Cr remains >25% above baseline; hold at lower dose if level is within 25% of baseline Whole-blood CSA trough level in children if inadequate clinical response or concomitant use of potentially interacting medications
Azathioprine	1-3 mg/kg/d Pediatric: 1-4 mg/kg/d	Baseline TPMT CBC/differential/platelets Renal function Liver function Hepatitis B and C TB testing HIV if indicated HCG if indicated	CBC/differential/platelets, liver function, renal function twice/mo × 2 mo, monthly × 4 mo, then every other month and with dose increases HCG if indicated Annual TB testing	Dosing may be guided by TPMT enzyme activity
Methotrexate	7.5-25 mg/wk Pediatric: 0.2-0.7 mg/kg/wk Consider test dose: 1.25-5 mg Check CBC in 5-6 d; if normal, increase dose gradually to desired therapeutic effect	CBC/differential/platelets Liver function Renal function Hepatitis B and C TB testing HIV if indicated HCG if indicated Pulmonary function tests if indicated	CBC/differential/platelets, liver function weekly for 2-4 wk and 1 wk after each major dose increase, then every 2 wk for 1 mo and every 2-3 mo while on stable doses Renal function every 6-12 mo Annual TB testing HCG as indicated	Liver enzymes transiently increase after MTX dosing; obtain laboratory results 5-7 d after the last dose Significant elevations of liver enzymes: - Exceeding ×2 normal, check more frequently - Exceeding ×3 normal, reduce the dose and recheck - Exceeding ×5 normal, discontinue Avoid in patients at risk for hepatotoxicity Liver biopsy may be considered at 3.5-4.0 g of cumulative MTX in adults No standard liver biopsy recommendations for children Consider pulmonary function tests before initiation and during therapy in consultation with a pulmonologist for patients with asthma or chronic cough, or consider alternative therapies CXR if respiratory symptoms arise

Mycophenolate mofetil	1.0-1.5 g orally twice daily Pediatric: 1200 mg/m^2 daily, which corresponds to 30-50 mg/kg/d	CBC/differential/platelets Renal function Liver function TB testing HIV if indicated HCG if indicated	CBC/differential/platelets, liver function every 2 wk for 1 mo; then monthly for 3 mo; then every 2-3 mo thereafter HCG if indicated Annual TB testing

CBC, Complete blood cell count; *Cr*, creatinine; *CSA*, cyclosporine; *CXR*, chest radiograph; *HCG*, human chorionic gonadotropin; *K+*, potassium; *Mg+*, magnesium; *MTX*, methotrexate; *TB*, tuberculosis; *TPMT*, thiopurine methyltransferase.

formulation demonstrated more rapid onset of action and greater initial efficacy relative to the conventional formulation in 1 double-blind, cross-over study.[40] Modified microemulsion formulation of CSA is not bioequivalent to the nonmodified formulation (both are available in oral capsules and solution), and the medications should not be used interchangeably.

The long-term effectiveness of CSA for AD cannot be determined based on the current literature. Data on relapse after CSA discontinuation are limited.[41] Lower dose protocols for a longer duration of treatment (maximum duration discussed below), independent of body weight, may be effective. In general, once clearance or near-clearance is achieved and maintained, CSA should be tapered or discontinued, with maintenance of remission via emollients, topical agents, and/or phototherapy.

Oral CSA should be administered in divided doses twice daily and taken at the same time every day for maximum benefit.

Adverse effects and monitoring

The side-effect profile of CSA is well known and is similar in patients with AD as with other cutaneous disorders. Potential adverse effects include: infection, nephrotoxicity, hypertension, tremor, hypertrichosis, headache, gingival hyperplasia, and increased risk of skin cancer and lymphoma. Thus, patients receiving CSA should be monitored for such potential consequences. These adverse effects may occur regardless of daily dosage used, but high-dose groups and low-dose groups have only been compared and measured over short periods of time (up to 12 weeks).[39] Some studies showed higher serum creatinine levels in patients given higher doses initially, but this trended downward over time to match the low-dose counterparts.[39]

Caution is advised when using CSA in patients on other systemic medications because of drug interactions. Consulting up-to-date product information and drug reference resources is suggested before prescribing this medication or when adding other medications in the course of treatment, to determine the safety profile for an individual patient. The US Food and Drug Administration (FDA) recommended time limit for consecutive use of CSA for psoriasis is currently 1 year, although longer-term use has been documented for other dermatologic conditions.[42]

Pediatric considerations

CSA is an effective treatment for AD in the pediatric population, similar to adults. Both continuous long-term (up to 12 months) and intermittent short-term dosing schemes (3- or

Table IX. Adverse effects, interactions, and contraindications of selected systemic immunomodulatory agents

Drug	Potential toxicities	Interactions	Contraindications
Cyclosporine	Pregnancy category C Renal impairment Hypertension Headache, tremor, paresthesia Hypertrichosis Gingival hyperplasia Nausea, vomiting, diarrhea Flu-like symptoms - Myalgias, lethargy Hypertriglyceridemia Hypomagnesemia Hyperkalemia Hyperbilirubinemia Increased risk of infection Risk of malignancies - Cutaneous - Lymphoproliferative	Medications that increase cyclosporine levels - Antifungals: ketoconazole, itraconazole, fluconazole, voriconazole - Diuretics: furosemide, thiazides, carbonic anhydrase inhibitors - Calcium channel antagonists: diltiazem, nicardipine, verapamil - Corticosteroids: high-dose methylprednisolone - Antiemetics: metoclopramide - Antibiotics: macrolides, fluoroquinolones - Antiarrhythmics: amiodarone - Antimalarials: hydroxychloroquine, chloroquine - Anti-HIV drugs: ritonavir, indinavir, saquinavir, nelfinavir - SSRIs: fluoxetine, sertraline Medications that decrease cyclosporine levels - Antibiotics: nafcillin, rifabutin, rifampin, rifapentine - Antiepileptics: carbamazepine, phenytoin, phenobarbital, valproic acid - Somatostatin analogs: octreotide - Tuberculostatics: rifampicin - Retinoids: bexarotene - St John wort: Hypericum perforatum - Others: octreotide, ticlopidine, bosentan Medications that may increase risk of renal toxicity - NSAIDs: diclofenac, naproxen, sulindac, indomethacin - Antifungals: amphotericin-B, ketoconazole - Antibiotics: ciprofloxacin, vancomycin, gentamycin, tobramycin, trimethoprim - Alkylating agents: melphalan - Others: H2 receptor histamine antagonists, tacrolimus Medications for which levels increase if taken with cyclosporine - Calcium channel blockers: diltiazem, nicardipine, verapamil - Erectile dysfunction drugs: sildenafil, tadalafil, vardenafil - Statins: atorvastatin, lovastatin, simvastatin - Benzodiazepines: midazolam, triazolam - Others: prednisolone, digoxin, colchicine, digoxin, diclofenac, bosentan	Caution Concomitant PUVA or UVB History of significant PUVA or radiation Concomitant MTX or other immunosuppressive agents Coal tar Major infection Poorly controlled diabetes Absolute Abnormal renal function Uncontrolled hypertension Malignancy Hypersensitivity to cyclosporine Killed vaccines may have decreased efficacy Live vaccines may be contraindicated*

Azathioprine	Pregnancy category D Bone-marrow suppression Increased risk of infections Nausea, vomiting, diarrhea Hypersensitivity syndrome Pancreatitis Hepatitis Risk of malignancies - Cutaneous - Lymphoproliferative	Allopurinol increases risk of pancytopenia, must reduce azathioprine dose by 75% Captopril increases risk of anemia and leukopenia Warfarin effect is reduced Pancuronium effect is reduced Cotrimoxazole increases risk of hematologic toxicity Rifampicin decreases azathioprine efficacy; hepatotoxic Clozapine increases risk of agranulocytosis	Absolute Allergy to azathioprine Pregnancy or attempting pregnancy Clinically significant active infection Relative Concurrent use of allopurinol Prior treatment with cyclophosphamide or chlorambucil Live vaccines may be contraindicated*
Methotrexate	Pregnancy category X Elevated liver enzymes Cytopenias Interstitial pneumonitis Pulmonary fibrosis Ulcerative stomatitis Nausea, vomiting, diarrhea Malaise, fatigue Chills and fever Dizziness Risk of infection GI ulceration and bleeding Photosensitivity Alopecia Risk of malignancies - Cutaneous - Lymphoproliferative	Hepatotoxic drugs: eg, barbiturates Sulfamethoxazole, NSAIDs, and penicillins (interfere with renal secretion of MTX) Folic acid antagonists: eg, trimethoprim	Absolute Pregnancy Nursing mothers Alcoholism Alcoholic liver disease Chronic liver disease Immunodeficiency Bone-marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia Hypersensitivity to MTX Relative Abnormalities in renal function Abnormalities in liver function Active infection Obesity Diabetes mellitus Live vaccines may be contraindicated*

Continued

Table IX. Cont'd

Drug	Potential toxicities	Interactions	Contraindications
Mycophenolate mofetil	Pregnancy category D GI most common - Diarrhea, nausea, vomiting, abdominal cramps Hematologic - Leukopenia, anemia, thrombocytopenia Genitourinary - Urgency, frequency, dysuria, sterile pyuria Increased incidence of infections Progressive multifocal leukoencephalopathy Hypercholesterolemia Hypophosphatemia Hyperkalemia Hypokalemia Fever, headache, myalgias Insomnia Peripheral edema Hypertension Risk of malignancies - Cutaneous - Lymphoproliferative	Antacids containing aluminum and magnesium Calcium and iron Cholestyramine Antibiotics (cephalosporins, fluoroquinolones, macrolides, penems, penicillins, sulfonamides) decrease MMF levels High-dose salicylates Phenytoin Xanthine bronchodilators Probenecid Acyclovir, ganciclovir, valganciclovir	Hypersensitivity to MMF and mycophenolic acid Live vaccines may be contraindicated* Pregnancy or attempting pregnancy

GI, Gastrointestinal; *MMF*, mycophenolate mofetil; *MTX*, methotrexate; *NSAIDS*, nonsteroidal anti-inflammatory drugs; *PUVA*, psoralen plus ultraviolet A; *SSRI*, selective serotonin reuptake inhibitor; *UV*, ultraviolet.

Adapted with permission.[42]

*Live vaccines may be contraindicated dependent on medication, dose, and the type of vaccine to be administered. Please reference up-to-date vaccine contraindication recommendations.

6-month courses) are efficacious. Although continuous dosing is associated with better efficacy and longer sustained effects relative to intermittent use, dosing regimens should be determined on an individual basis.[43] As with adult patients, the lowest effective dose to achieve the desired results should be given.

AZATHIOPRINE

AZA is a purine analog that inhibits DNA production, thus preferentially affecting cells with high proliferation rates, such as B cells and T cells during inflammatory disease states. Although it is FDA approved for the treatment of rheumatoid arthritis and renal transplant rejection prophylaxis, it is also used off-label to treat other inflammatory cutaneous and systemic disorders, including AD.

AZA is recommended as a systemic agent for the treatment of refractory AD. Further details regarding the administration of AZA can be found in Tables VIII and IX, and the strength of recommendation is summarized in Table III.

Efficacy

AZA is efficacious in treating AD. Meggitt et al[44] compared the effectiveness of AZA with placebo in a parallel-group, double-blinded trial of moderately to severely affected patients with AD. After 12 weeks, the AZA-treated group reported a 37% improvement in their dermatitis, relative to 20% improvement with placebo (17% difference; 95% confidence interval 4.3-29), as measured by the Six Area, Six Sign AD (SASSAD) scoring system. Similarly, a 2002 publication by Berth-Jones et al[45] found a SASSAD score reduction of 26% in AZA-treated patients relative to 3% reduction while treated with placebo in their double-blind, placebo-controlled study ($P < .01$). These data demonstrate that AZA improves both QOL and signs and symptoms of disease when used in patients with AD as monotherapy.

Dosage and scheduling

As with other systemic medications, the dose range of AZA given to patients with AD is variable, with most studies choosing a dose range between 1 to 3 mg/kg/d. Whether this range is optimal for patients with AD is yet unknown based on the available data. Graduated dosing to maximize benefit while limiting side effects is preferred, as a considerable number of patients develop intolerable nausea and vomiting at higher doses and electively discontinue the medication.[44,45] Dosing using thiopurine methyltransferase (TPMT) activity level may also be helpful (discussed below). A delayed effect may be noted, with some patients needing 12 weeks or greater of medication to achieve full clinical benefit. Once clearance or near-clearance is achieved and maintained, AZA should be tapered or discontinued, with maintenance of remission via emollients and topical agents. Concomitant phototherapy is not advised because of increased risk of DNA damage and possible photocarcinogenicity, particularly with UVA exposure.[46]

AZA is currently available in the United States in tablet form only, although liquid formulations can be compounded. It may be given once daily.

Adverse effects and monitoring

The side-effect profile of AZA is well known and similar for patients with AD as for other patients taking the medication for cutaneous indications. Nausea, vomiting and other gastrointestinal (GI) symptoms (bloating, anorexia, cramping) are common while on AZA, and may cause patient dissatisfaction and noncompliance. Other side effects that have been variably reported include: headache, hypersensitivity reactions, elevated liver enzymes, and leukopenia. These potential side effects must be taken into consideration in individual patients, with a thorough history, physical examination, and laboratory monitoring performed as deemed appropriate before and during therapy. Although an increased risk of infection, lymphoma, and nonmelanoma skin cancer development has been noted on some patients treated with AZA for other conditions, these patient populations usually require polypharmacy for their disorders, confounding the true relevance to AZA use. There are no studies to date that signify such a risk for patients with AD using long-term therapy, although the available data are largely uncontrolled and use is generally limited to a few years.

The metabolism of AZA is dependent on an individual's TPMT activity level, a principle enzyme in the thiopurine pathway. Genetic polymorphisms in TPMT activity are linked to a patient's susceptibility to AZA toxicity, such that the homozygous carrier state of low or absent enzyme capacity poses the greatest toxicity risk.[44,45] Thus, baseline TPMT level testing is strongly recommended before AZA initiation, with avoidance of use in those with very low or absent enzyme activity. Although TPMT enzyme activity will not alter the risk of GI intolerance or hypersensitivity syndrome, greater TPMT activity reduces the risk of myelotoxicity. Testing for TPMT may also enhance efficacy by preventing underdosing in those patients who have high enzymatic function. It should be noted TPMT is an inducible enzyme, such that levels have been reported to change over time.[47,48] Regular

monitoring of the patient's blood cell count[45,49] and liver enzymes is also essential while taking AZA, regardless of TPMT status.

Pediatric considerations

There is literature to support the use of AZA to treat AD in the pediatric population. Use is generally recommended for those children whose dermatitis is recalcitrant, or when there is significant psychosocial impact on the patient and family unit.[50,51] Insufficient data exist to recommend an optimal dose, duration of therapy, or to predict the relapse rate upon discontinuation. However, the most common dosage given is 2.5 mg/kg/d, with a higher treatment range maximum of 4 mg/kg/d relative to adult dosing (maximum 3 mg/kg/d). TPMT levels should be measured in pediatric patients at baseline, with repeated testing considered in cases of nonresponse or change in response. Evidence shows those children with higher TPMT levels may respond less well to treatment but may have a greater risk of hepatotoxicity.[50] Similarly, children with lower TPMT levels may have improved clinical response on lower drug doses but may have an increased risk of myelosuppression.

METHOTREXATE

MTX is an antifolate metabolite and blocks the synthesis of DNA, RNA, and purines. It is also thought to negatively affect T-cell function. It is currently FDA approved for several oncologic and inflammatory disorders, including dermatologic conditions such as advanced mycosis fungoides and psoriasis. Its many off-label uses include AD. MTX is recommended as a systemic agent for the treatment of refractory AD. Further details regarding the administration of MTX can be found in Tables VIII and IX, and the strength of recommendation is summarized in Table III.

Efficacy

The true efficacy of MTX in the treatment of refractory AD is unknown, as there is inconsistency between studies regarding methods, dosing, and duration of therapy. One open-label, dose-ranging, prospective trial of MTX for the treatment of moderate to severe AD in adults demonstrated a disease activity reduction of 52% from baseline via SASSAD scoring (confidence interval 45%-60%).[52] The medication was given for 24 weeks, and patients were followed up for an additional 12 weeks after MTX discontinuation. MTX was well tolerated, and patients noted improvement in sleep and decreased pruritus. Mean disease activity remained at 34% below baseline at the end of the follow-up period. Another single-blind trial by Schram et al[33] randomized individuals to take either MTX (10-22.5 mg/wk) or AZA (1.5-2.5 mg/kg/d) over a 24-week period. At 12 weeks of therapy, both the MTX group and the AZA group had statistically significant clinical improvement (severity scoring 42% and 39%, respectively, $P = .52$). No adverse events occurred in the study, and the medications were deemed equally efficacious in the treatment of severe AD. Lyakhovitsky et al[53] successfully administered low-dose MTX (10-25 mg per week) to 20 adult patients with AD, with improvements in both the SCORing AD (SCORAD) and the Dermatology Life Quality Index measurements. MTX appears safe, well tolerated, and effective for controlling severe AD. Additional randomized, controlled studies are warranted to determine the optimal dose range and magnitude of response.

Dosage and scheduling

MTX is readily available in solution (for intramuscular or subcutaneous injection) and oral tablet form. Patients typically prefer to avoid injection of the medication but bioavailability is better in this form; fortunately, 0.1 mL of the 25 mg/mL injection solution is equivalent to a 2.5 mg oral tablet, making conversion between the 2 formulations straightforward when necessary. Judicious measuring is strongly suggested to ensure that the appropriate amount of medication is given to the patient. MTX is usually given as a single weekly dose. The dose range for MTX in patients with AD is extrapolated from its use in psoriasis, and is between 7.5 and 25 mg weekly.[42] Divided dosing, given every 12 hours for 3 doses, is an alternative method for dosing MTX. The provider needs to adjust the dose appropriately if this schedule is to be used.

As with other systemic medications, dosing should be tailored to the individual patient to achieve and maintain adequate disease control. The average time to maximum effect averages 10 weeks, with minimal to no further efficacy after 12 to 16 weeks with further dose escalation.[42,52,53] Once clearance or near-clearance is achieved and maintained, MTX should be tapered or discontinued, with maintenance of remission with emollients and topical agents and/or phototherapy. Nonresponding patients on a sufficient dose ($\geq$15 mg/wk) of MTX may consider discontinuing therapy after a 12- to 16-week trial.

Adverse effects and monitoring

There are very limited data that address the safety of MTX use in patients with AD specifically.

The side-effect profile of MTX is well known, however, and thought to be similar in patients with AD as with others taking the medication for other cutaneous indications. Nausea and other GI symptoms may preclude oral administration. Such symptoms usually abate when given parenterally. Severe adverse effects, including bone-marrow suppression and pulmonary fibrosis, can occur. Literature suggests bone-marrow suppression is often reversible upon MTX dose reduction or discontinuation.[52,53] Risk for skin cancer and lymphoma has been reported, although some cases of lymphoma arising during low-dose treatment have regressed on drug discontinuation. Pulmonary fibrosis may occur with short- or long-term use of the medication, such that patients with pulmonary diseases (eg, asthma, chronic cough) may not be candidates. If MTX is considered in such patients, they should undergo pulmonary function studies in consultation with a pulmonologist before drug initiation.

Although the cumulative dose of MTX given to an individual should be documented in the medical record, its relevance to monitoring for hepatic toxicity (including potential liver biopsy) in patients with AD is unclear and cannot be directly postulated from its relevance in patients with psoriasis.[42,54] In contrast to patients with AD, patients with psoriasis typically have more comorbidities, including obesity, and may practice polypharmacy to a greater extent than their AD counterparts. A 2009 Consensus Conference on MTX use in patients with psoriasis suggests patients being considered for MTX therapy be divided into 2 groups, those without underlying risk factors for hepatotoxicity, and those with risk factors.[54] This group of experts advised liver biopsy should be considered in patients at low risk after a cumulative dose of 3.5 to 4 g. The aminoterminal peptide of procollagen 3 is used in Europe (but is generally not available in the United States) as a test for hepatic fibrosis, reducing the need for frequent liver biopsies. Folic acid supplementation is recommended for all patients with AD taking MTX to reduce the likelihood of hematologic and GI toxicity. Data do not support 1 specific regimen. In general, expert consensus suggests 1 mg/d, with a possible escalation up to 5 mg/d, depending on a patient's unique medical needs. Patients may skip folate supplementation on the day of MTX intake.

Pediatric considerations

At the time of literature review, there were no prospective data on MTX use in children for the treatment of AD. Since then, a 12-week study showed a slower onset of effect compared with low-dose cyclosporine, but increased time before relapse on discontinuation.[55] Multiple studies regarding its use in pediatric patients with psoriasis show MTX to be a safe, effective, and well-tolerated medication.[56] The side-effect profile for children on MTX commonly includes GI symptoms such as stomatitis, nausea, and vomiting, but the same potential risks exist in children as they do in adults. Most adverse effects of MTX are reversible upon dose reduction, route modification, or altered dosing schedule. As with adult patients, the lowest effective dose to achieve the desired results should be given.

MYCOPHENOLATE MOFETIL

MMF is an immunosuppressant that blocks the purine biosynthesis pathway of cells via the inhibition of inosine monophosphate dehydrogenase. MMF selectively affects B cells and T cells, as other cells have purine scavenger mechanisms that compensate for this blockage, giving this medication a unique mechanism of action to treat inflammatory disorders. Although it is FDA approved solely for solid organ transplant rejection prophylaxis, it is recognized as an off-label systemic therapy option in patients with AD and should be considered as an alternative, variably effective therapy for refractory cases. Further details regarding the administration of MMF can be found in Tables VIII and IX, and the strength of recommendation is summarized in Table III.

Efficacy

Aggregate data on MMF use to treat AD are highly variable but overall suggest that MMF is an alternative therapy for refractory AD. Efficacy is inconsistent. Haeck et al[34] treated 55 adult patients with severe AD with CSA for 6 weeks, and then subsequently switched 24 of these patients from CSA to MMF for 30 weeks. Both CSA- and MMF-treated patients were monitored during this time period, and for 12 weeks after medication discontinuation. During the initial 10 weeks of MMF use, the SCORAD measurements were better for the patients who remained on CSA, and 7 patients in the MMF cohort required a limited oral corticosteroid course. Thereafter, efficacy was equal in both treatment groups, and side effects were comparable, mild, and temporary. This suggests the initial response to MMF was delayed, with improvement as drug levels increased. Clinical remission lasted longer for patients treated with MMF relative to those treated with CSA upon medication discontinuation.

In a retrospective chart analysis, Murray and Cohen[57] reviewed 20 adult patients with moderate

to severe AD who were treated with MMF. Seventeen patients (85%) reported disease improvement within the first month of administration. Ten patients (50%) achieved disease clearance and were able to discontinue the medication.

Dosage and scheduling

Insufficient data exist to make recommendations regarding the optimal MMF dosing or duration of therapy for patients with AD. Dosing ranges from 0.5 to 3 g/d.[57] The relapse rate after withdrawal is also unknown.

MMF is available in oral suspension, capsules, and tablets, and is given twice daily.

Adverse effects and monitoring

MMF is generally well tolerated, with nausea, vomiting, and abdominal cramping being the most common side effects. These GI symptoms may improve if the patient takes the enteric-coated formulation. The development of GI symptoms, along with headaches and fatigue, are not dose dependent and do not tend to negatively impact compliance. Rarely, hematologic (anemia, leukopenia, thrombocytopenia) and genitourinary (urgency, frequency, dysuria) symptoms have been reported. There is a theoretical risk of increased susceptibility to viral and bacterial infections while taking MMF, as is clearly observed in patients with organ transplantation. The applicability of this risk to patients with AD is unknown. Similar to other immunosuppressive drugs, cutaneous malignancy and lymphoma are potential risks, although difficult to delineate for MMF given many reports involve multidrug therapy.

Pediatric considerations

MMF should be considered a relatively safe alternative systemic therapy for pediatric patients with refractory AD. Patients aged 2 years and older have been treated with MMF as monotherapy for severe AD with benefit and without hematologic, hepatic, or infectious sequelae.[58] The suggested dosing in children of 600 to 1200 mg/m^2 is based on body surface area secondary to increased hepatic metabolism in this patient population. This equates to 40 to 50 mg/kg/d in young children and 30 to 40 mg/kg/d in adolescents. No long-term efficacy or safety profiles exist at this time, although use in children for up to 24 consecutive months has been reported for AD without deleterious effects.

INTERFERON GAMMA

Interferon gamma (IFN-G) is a cytokine with a principle role in the innate and adaptive immune system cascade, enhancing natural killer cell production and increasing macrophage oxidation. It is classified pharmacologically as a biologic response modifier, and is FDA approved for chronic granulomatous disease and malignant osteopetrosis. IFN-G is moderately and variably effective for severe AD in clinical trials, but may be considered as an alternative therapy for refractory AD in adults and children who have not responded to, or have contraindications to, other systemic therapies or phototherapy. The strength of recommendation for IFN-G is summarized in Table III.

Efficacy

There are a few studies on IFN-G that demonstrate its efficacy in the treatment of AD. One randomized, placebo-controlled, double-blinded trial published in 1993 compared 38 patients with AD receiving daily subcutaneous injections of IFN-G with 40 patients receiving placebo injections over 12 weeks.[59] Statistically significant improvements were found in patients treated with IFN-G versus placebo with regards to erythema (P = .035), excoriations and erosions (P = .045), and conjunctivitis ($P < .002$). A study by Jang et al[60] treated 41 patients with IFN-G via subcutaneous injection 3 times weekly for 12 weeks, versus 10 patients who received placebo injections. These patients treated with IFN-G also had notable improvement in clinical disease activity compared with placebo ($P < .05$).

Dosage and scheduling

There is no recommended optimal dose of IFN-G for the treatment of AD. Dosages for FDA-approved indications are based on body surface area, for both adults and children, and are usually administered 3 times weekly.

IFN-G is available solely in solution form for subcutaneous injection.

Adverse effects

Constitutional side effects (fatigue, fever, nausea, vomiting, myalgia) have been documented with its use.[59]

Monitoring

Recommended monitoring for those taking IFN-G for chronic granulomatous disease or osteopetrosis includes pretreatment blood chemistries (complete blood cell count with differential, renal function serologies, hepatic function serologies) and urinalysis, repeated every 3 months during treatment. Similar monitoring should be considered for patients with AD receiving IFN-G.

Pediatric considerations

There are no specific recommendations unique to the pediatric population.

SYSTEMIC STEROIDS

Corticosteroids are natural products of the adrenal gland, used to regulate the immune system and stress response in human beings. Although systemic steroids are used by some providers to treat AD because they rapidly improve clinical symptoms, caution is warranted to ensure their administration is time-limited and judicious. Rebound flare and increased disease severity is a commonly observed phenomenon upon discontinuation of systemic steroids. Thus, although temporarily effective, systemic steroids (oral or parenteral) should generally be avoided in adults and children with AD because the potential short- and long-term adverse effects, described below, largely outweigh the benefits. Systemic steroids may be considered for short-term use in individual cases whereas other systemic or phototherapy regimens are being initiated and/or optimized. The strength of recommendation of systemic steroids is summarized in Table III.

Efficacy

The efficacy of systemic steroids to decrease clinical symptoms of AD is commonly accepted and frequently observed, but there are few reports in the literature to support it.[4,35] A double-blind, placebo-controlled study by Schmitt et al[35] compared patients on prednisolone with those taking CSA or placebo. All patients remained on primary therapy, such as topical steroids and emollients. In this trial, only 1 patient of 27 taking prednisolone achieved a durable remission, defined as a greater than 75% improvement in baseline SCORAD measurement after 2 weeks of oral steroid therapy and a 4-week follow-up time period. This study was also prematurely discontinued because of significant rebound flaring in the prednisolone group.

Systemic steroids are discouraged for continuous or chronic intermittent use in AD but may be considered for acute usage as a transitional therapy in severe, rapidly progressive, or debilitating cases in adults or children, while nonsteroidal immunomodulatory agents or phototherapy is being initiated. Although immediate improvement of AD may be noted by patients and providers, other systemic medications with a more favorable side-effect profile should be considered in lieu of chronic systemic steroids.

Dosage and scheduling

The most commonly used formulations of systemic steroids in patients with AD are prednisone, prednisolone, and triamcinolone acetonide. Prednisone and prednisolone are available as a tablet or oral solution for enteral administration, whereas triamcinolone acetonide is available as a suspension for intramuscular injection. Dosing is based on body weight, but as a general principle most providers using a dosage range of 0.5 to 1.0 mg/kg.[35] A taper is indicated to decrease the risk of adrenal suppression. Regardless of the taper schedule, flare of the dermatitis upon steroid discontinuation may be expected.

Adverse effects

The short- and long-term side effects of systemic steroids are well documented. The likelihood of undesired side effects in patients treated for AD is unknown but is thought to be similar to other patients taking the medication. These adverse effects include: hypertension, glucose intolerance, gastritis, weight gain, decreased bone density, adrenal suppression, and emotional lability. Pediatric patients experience decreased linear growth while on the medication.[61] Patients on long-term protocols may need antibiotic prophylaxis for opportunistic infections, calcium and vitamin D supplementation, and immunizations according to a booster ("catch-up") schedule. Patients with AD who experience a rebound flare upon steroid discontinuation may become frustrated when the disease is difficult to manage. When systemic steroids are given for an AD exacerbation or for another indication in a patient with AD, a taper schedule is required.

Monitoring

Patients on long-term systemic steroids may require blood pressure monitoring, ophthalmologic examination, hypothalamic-pituitary-adrenal axis suppression testing, bone-density evaluation (adults), and growth-velocity measurement (children).

Pediatric considerations

Children and adolescents given systemic steroids can experience decreased linear growth while on the medication.[61]

All potential adverse effects of systemic steroids in adults may also be observed in children. Systemic steroids are not recommended for children with AD unless they are required to manage comorbid conditions (eg, asthma exacerbations), or are given as part of a short-term transition protocol to nonsteroidal systemic immunomodulatory agents. Children on long-term systemic steroids may require

booster immunization protocols because of a robust vaccination schedule relative to adults.

OMALIZUMAB

Limited data exist to determine the efficacy of omalizumab in the treatment of AD. One double-blind, placebo-controlled study did not show clinical improvement in AD with its use despite reducing free serum IgE levels.[62]

ORAL CALCINEURIN INHIBITORS

Tacrolimus and pimecrolimus are available in topical formulations for the treatment of AD with proven efficacy. At this time, tacrolimus is available in the United States in oral capsule and intravenous solution formulations for transplant rejection prophylaxis. Pimecrolimus is currently available in topical form only. Insufficient data exist to recommend the use of systemic calcineurin inhibitors in the management of AD.[63]

OTHER SYSTEMIC THERAPIES

There are insufficient data at this time to make a recommendation for the use of tumor necrosis factor-alpha inhibitors, intravenous immunoglobulin, theophylline, papaverine, or thymopentin in the management of AD.

ANTIMICROBIALS

Because of an impaired skin barrier, patients with AD are predisposed to secondary bacterial and viral infection, most commonly with *Staphylococcus aureus* and HSV. Although *S aureus* can be cultured from the skin of an estimated 5% of the population without dermatitis, this microbe is isolated from greater than 90% of adult patients with AD upon skin culture.[64] The clinical relevance of bacterial overgrowth is patient dependent, as most patients with AD do not show increased morbidity from the *Staphylococcus* colonization. This can provide a diagnostic challenge to the provider, as the clinical appearance of active localized infection and active AD can be difficult to distinguish. Certain clinical signs, such as crusting, may be present in either localized infection or active dermatitis. The presence of purulent exudate and pustules on skin examination may suggest a diagnosis of secondary bacterial infection over inflammation from dermatitis. Less frequently, the compromised skin barrier allows infection with HSV, referred to as "eczema herpeticum," a dermatologic urgency because of its increased patient morbidity.

Although the use of systemic antibiotics in the treatment of noninfected AD is not recommended, they can be recommended for use in patients with clinical evidence of bacterial infection. Antibiotics may be administered in addition to standard, suitable treatment for AD, including the concurrent application of topical steroids.[64,65] Similarly, systemic antiviral agents should be used in the treatment of eczema herpeticum.

Table X. Recommendations for the use of systemic antimicrobials

The use of systemic antibiotics in the treatment of noninfected atopic dermatitis is not recommended.
Systemic antibiotics are appropriate and can be recommended for use in patients with clinical evidence of bacterial infections in addition to standard and appropriate treatments for atopic dermatitis disease itself (which may include the concurrent use of topical corticosteroids).
Systemic antiviral agents should be used for the treatment of eczema herpeticum.

Recommendations for the use of systemic antimicrobials in the management of AD are summarized in Table X, and the strength of recommendation is summarized in Table III.

Efficacy

There are numerous studies addressing the efficacy of systemic antibiotics to decrease *S aureus* colonization rates in patients with AD; however, data on the impact of this treatment on AD disease outcomes are limited. A Cochrane analysis from 2010 was able to use 3 of the studies (involving 103 total patients).[65] This review concluded that the use of systemic antistaphylococcal medications is warranted in overtly infected patients with AD only; the use of topical or systemic antibiotics as a therapy for uninfected or colonized dermatitic skin is controversial. The colony count is reduced in patients with AD treated with topical or systemic antibiotics, but counts return to previous levels within days to weeks of medication discontinuation.[64-67] Furthermore, antigens from *Staphylococcus* may persist for prolonged periods of time after eradication, and incomplete elimination may increase bacterial resistance to previously susceptible treatments. Thus, the judicious use of antibiotics, reserved for frank bacterial infections, is suggested. Skin culture with bacterial antibiotic susceptibility profiling may be appropriate for recurrent or nonresponsive infections.

The treatment of eczema herpeticum with systemic antiviral medications has significantly altered the course of this once potentially fatal condition. Before the use of acyclovir, there was a 10% to 50% mortality for patients with untreated

eczema herpeticum.[68] Aronson et al[68] demonstrate in a retrospective chart review of 1331 children from 42 tertiary care pediatric hospitals that no deaths occurred from eczema herpeticum when patients received systemic antiviral therapy. Timing of acyclovir initiation was also directly related to length of hospital course, with earlier medication initiation decreasing length of stay, further supporting acyclovir's efficacy in eczema herpeticum treatment.

Dosage and scheduling

There are several antibiotics that have antimicrobial properties against *S aureus*, with various mechanisms of action. Similarly, there are now multiple systemic antiviral medications for the treatment of HSV. Dosage and scheduling should be based on each individual medication's drug profile.

Adverse effects and monitoring

Adverse effects from systemic antimicrobials, and the need for laboratory monitoring, are dependent on the medication chosen and the patient's medical history. Consulting current product information and drug reference material is suggested before prescribing a particular medication to determine its safety profile, indications, and contraindications for an individual patient.

Pediatric considerations

There are no specific recommendations unique to the pediatric population.

ORAL ANTIHISTAMINES

Histamine is a protein secreted by mast cells and basophils as a component of the immune system response to foreign antigen presentation. The primary function of histamine is to stimulate local blood vessels and nerves, producing vasodilatation and pruritus. Patients with AD often report itch as burdensome, affecting their QOL.[69-72] Secondary scratching not only intensifies pruritus (the "itch-scratch cycle") but also further compromises the skin barrier. Oral antihistamines have been used in the management of pruritus in patients with AD in an effort to improve their QOL by inhibiting these vascular and neurologic effects, but there is insufficient evidence to recommend the general use of antihistamines as part of the treatment of AD. Short-term, intermittent use of sedating antihistamines may be beneficial in the setting of sleep loss secondary to itch, but should not be substituted for management of AD with topical therapies.

Table XI. Recommendations for the use of systemic antihistamines

There is insufficient evidence to recommend the general use of antihistamines as part of the treatment of atopic dermatitis.
Short-term, intermittent use of sedating antihistamines may be beneficial in the setting of sleep loss secondary to itch, but should not be substituted for management of atopic dermatitis with topical therapies.
Nonsedating antihistamines are not recommended as a routine treatment for atopic dermatitis in the absence of urticaria or other atopic conditions such as rhinoconjunctivitis.

Recommendations for the use of oral antihistamines in the management of AD are summarized in Table XI, and the strength of recommendation is summarized in Table III.

Efficacy

There are numerous randomized, controlled trials that have examined whether systemic antihistamines benefit AD as a disease process, and whether their effects specifically benefit patients with AD via itch relief. Both sedating and nonsedating medications have been studied. The evidence is mixed and favors no benefit, with many patients reporting as much improvement with placebo.[73] Klein and Clark[71] reviewed 16 randomized, controlled trials of various sizes and concluded that nonsedating histamines are ineffectual in AD management, whereas sedating forms may improve sleep quality. In the Early Treatment of the Atopic Child trial, infants 12 to 24 months of age were randomized to receive cetirizine or placebo for 18 months.[69] Although cetirizine-treated patients had less urticaria during this time period, there was no statistically significant improvement in overall AD control. Similarly, a dose-ranging study of 178 adults demonstrated a 4-fold dose of cetirizine (40 mg daily) was necessary to significantly improve erythema, lichenification, body surface area involvement, and pruritus in their cohort.[72] Doubling the recommended dose (20 mg daily) improved pruritus only. These results are attributed to a sedating effect of cetirizine when given in a dose higher than usually recommended.

Dosage and scheduling

Oral antihistamines are available both over-the-counter and by prescription, depending on which medication is selected. Dosage and scheduling should be based on each individual medication's drug profile.

Adverse effects and monitoring

Adverse effects from systemic antihistamines are known and vary by the medication chosen and the patient's medical history. Common side effects include undesired sedation (including the nonsedating formulations) and anticholinergic symptoms (dry mouth, blurred vision, tachycardia). No laboratory monitoring is required. If antihistamine toxicity is suspected, an electrocardiogram should be obtained to assess for a dysrhythmia. Consulting current product information and drug reference material is suggested before prescribing a particular medication to determine its safety profile for an individual patient.

Pediatric considerations

The use of sedating antihistamines in school-age children may negatively affect school performance, warranting attention to dosage and scheduling.[74]

GAPS IN RESEARCH

In review of the currently available highest level of evidence, the expert work group acknowledges that much has yet to be learned about the management of AD via phototherapy and systemic medications. Significant gaps in research were identified, including but not limited to: comparative trials of various phototherapy methods and dosage protocols, maintenance requirements for phototherapy, comparative studies of systemic immunomodulating medications, optimal dose and duration of systemic immunomodulating medications, and drug trials in pediatric patients. It is hoped that additional knowledge of the pathophysiology of AD, particularly the mechanisms of pruritus, will lead to more optimal management options, improved disease control, and enhanced QOL for patients and their families.

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The below information represents the authors identified relationships with industry that are relevant to the guideline. Relevant relationships requiring recusal for the drafting of guideline recommendations are noted. The management of conflict of interest for this guideline complies with the Council of Medical Specialty Societies' *Code of Interactions with Companies*.

Dr Cohen served on the advisory boards and as a consultant for Ferndale Labs, Galderma, and Onset receiving honoraria; served on the board of directors and as a consultant for Brickell Biotechnology and Topica receiving honoraria, stock, and stock options; and was a consultant for Dermira and Dr Tattoff receiving honoraria and stock options. Dr Bergman served as a consultant for Pediapharm receiving honoraria. Dr Chamlin served on the advisory boards for Galderma, Promius, and Valeant receiving honoraria. Dr Cooper served on the Board of Directors for the American Academy of Dermatology receiving no compensation. Dr Feldman served on the advisory boards for Amgen, Doak, Galderma, Pfizer, Pharmaderm, Skin Medica, and Stiefel receiving honoraria; was a consultant for Abbott, Astellas, Caremark, Coria, Gerson Lehrman, Kikaku, Leo Pharma, Medicis, Merck, Merz, Novan, Peplin, and Pfizer receiving honoraria, and Celgene, HanAll, and Novartis receiving other financial benefits; was a speaker for Abbott, Amgen, Astellas, Centocor, Dermatology Foundation, Galderma, Leo Pharma, Novartis, Pharmaderm, Sanofi-Aventis, Stiefel, and Taro receiving honoraria; served as a stockholder and founder for Causa Technologies and Medical Quality Enhancement Corporation receiving stock; served as an investigator for Abbott, Amgen, Anacor, Astellas, Basilea, Celgene, Centocor, Galderma, Medicis, Skin Medica, and Stiefel receiving grants, and Suncare Research receiving honoraria; and had other relationships with Informa, UptoDate, and Xlibris receiving royalty, and Medscape receiving honoraria. Dr Feldman recused himself for the drafting of guideline recommendations related to phototherapy. Dr Hanifin served on the advisory board for Chugai Pharma USA receiving honoraria; was a consultant for GlaxoSmithKline, Merck Elocon Advisory Board, Pfizer, and Valeant Elidel Advisory Board receiving honoraria; and served as an investigator for Asubio, Dohme, and Merck Sharp receiving grants. Dr Krol served as an investigator for Pierre-Fabre receiving grants. Dr Margolis served as a principal investigator for a Valeant postmarketing study. All sponsored research income was paid directly to his employer. Dr Paller served as a consultant to Anacor, Galderma, Leo Pharma, Promius, Sanofi/Regeneron, and TopMD receiving honoraria; and was an investigator for

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