Practice parameter

Atopic dermatitis: A practice parameter update 2012

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This parameter was developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma and Immunology. The AAAAI and the ACAAI have jointly accepted responsibility for establishing "Atopic dermatitis: a practice parameter update 2012." This is a complete and comprehensive document at the current time. The medical environment is a changing environment, and not all recommendations will be appropriate for all patients. Because this document incorporated the efforts of many participants, no single individual, including those who served on the Joint Task Force, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma & Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion. Published practice parameters of the Joint Task Force on Practice Parameters for Allergy & Immunology are available online at http://www.jcaai.org. (J Allergy Clin Immunol 2013;131:295-9.)

Key words: *Atopic dermatitis/atopic eczema, pathogenesis, genetics, diagnosis, management, therapy, triggers,* Staphylococcus*, quality of life, sleep, cyclosporine, immunomodulating agents, phototherapy, allergen immunotherapy*

To read the Practice Parameter in its entirety, please download the online version of this article from www.jacionline.org. Please note that all references cited in this print version can be found in the full online document.

PREFACE

Atopic dermatitis (AD) is often the first manifestation of allergic disease. Most patients with AD will also have another atopic disorder, such as allergic rhinitis, asthma, or food allergy. Therefore the evaluation and management of AD are an integral part of an allergist/immunologist's training and practice. It is also important for the primary care physician to understand the basis for effective evaluation and management of patients with this condition because AD affects more than 10% of children and can have a significant effect on quality of life for the patient and the family unit. As discussed in this document, it is also important for the primary care physician to know when to appropriately consult an AD specialist.

Since the last parameter on AD was published in 2004, there have been remarkable advances in the understanding of the genetics and pathophysiology of the disease.[1] Hypotheses on the cause of AD must now include epidermal barrier defects, as well as immune dysregulation of both the innate and adaptive immune systems. AD is a complex inflammatory process, our understanding of which is constantly undergoing revision as more data become available on the role of IgE-bearing Langerhans cells, atopic keratinocytes, monocytes/macrophages, eosinophils, and mast cells and their interaction with IL-4–, IL-5–, and IL-13–producing T_H2, regulatory T, and T_H22 lymphocytes. There is a complicated interaction between these cells and their products and susceptibility genes and the host environment, which leads to the clinical findings that characterize AD.

The major objective of this parameter is to improve the care of patients with AD. This should be accomplished by establishing

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boundaries for the evaluation and management of patients with this condition while reducing unwanted and unnecessary variation in treatment.

This updated parameter was developed by the Joint Task Force on Practice Parameters, which has published 33 practice parameters for the field of allergy/immunology, including the original parameter on AD. The current document builds on the 2004 parameter on AD. It was written and reviewed by subspecialists in allergy and immunology, as well as dermatology, and was supported by the 3 allergy and immunology organizations noted above. Therefore this document represents an evidence-based, broadly accepted consensus opinion.

The major decision points in the evaluation and management of AD are noted in Fig 1 and explained in the Annotations. Also included in this parameter are summary statements, which represent the key points in the evaluation and management of AD. These summary statements appear again before each section the online document, followed by text that supports the summary statement or statements. There are sections on definitions, immunopathology and genetics, clinical diagnosis, first-line management and treatment, identification and elimination of triggering factors, microbes, emotional stress, patient education, and treatment of the difficult-to-manage patient.

EXECUTIVE SUMMARY

AD is a genetically transmitted, chronic inflammatory skin disease that affects 10% to 20% of children and 1% to 3% of adults.[2,3] In the vast majority of patients, the disease develops before the age of 5 years, although it develops in adulthood in as many as 20% of patients.[4] AD is the first manifestation of atopy in many patients who later have allergic rhinitis, asthma, or both, a pattern that has been referred to epidemiologically as "the atopic march." Pruritus, scratching, and chronic, relapsing, or both eczematous lesions are major hallmarks of the disease. In infants and young children, there is a characteristic pattern of involvement of the face, neck, and extensor skin surfaces. In older children and adults, the skin lesions often involve lichenification and are usually localized to the flexural folds of the extremities. Factors that can exacerbate symptoms in patients with AD include temperature, humidity, irritants, infections, food, inhalant and contact allergens, and emotional stress. Food allergy has been implicated in approximately one third of children with AD, although specific IgE might be present (eg, food sensitization) without clinical features of food allergy.[5]

The diagnosis of AD is based on its clinical presentation rather than the results of diagnostic testing.[6,7] However, the judicious use of percutaneous skin tests or *in vitro* tests for the presence of specific IgE to relevant allergens is a sensitive way of identifying potential allergic triggering factors. Double-blind food challenges are often necessary to determine the relevance of specific food ingestion to symptoms.[8] The effective management of AD involves a combination of trigger avoidance, measures to restore skin barrier function, and anti-inflammatory medication. Trigger avoidance should be individualized based on a careful history and the results of specific IgE testing. Barrier function can be improved by careful hydration and moisturizer application, such as soaking in a warm bath for at least 10 minutes followed by the immediate application of a moisturizer.

There are multiple anti-inflammatory medication options available for treating AD.[9,10] Topical corticosteroids are appropriate for the vast majority of patients, and the potency of the corticosteroid chosen should be individualized based on the severity of the dermatitis, the location of the affected skin, the surface area of the affected skin, and the age of the patient.[11] Clinical exacerbations might require temporarily switching to a more potent topical agent for a short period of time. Topical tacrolimus and pimecrolimus are anti-inflammatory calcineurin inhibitors and second-line agents that have been approved for topical use in adults and children (≥2 years of age) with AD.[12-14] These agents interrupt activation of lymphocytes and other inflammatory cells, and they have become an integral part of treating AD.[15-17]

There are a variety of other treatment options for patients with severe or refractory AD. These include wet dressings and occlusion[18-20]; phototherapy[21,22]; systemically administered immunosuppressants, such as cyclosporine[23]; and antimetabolites.[24,25] In rare cases short-term hospitalization might be a useful way to temporarily reduce exposure to environmental and emotional triggers while initiating intensive patient education, diagnostic testing (eg, skin testing and food challenges), intravenous antibiotics (if indicated), and aggressive topical treatment.

SUMMARY STATEMENTS

Definitions

Summary Statement 1: AD is a familial, chronic inflammatory skin disease that commonly presents during early infancy and childhood but can persist or start in adulthood. (C)

Immunopathology and genetics

Summary Statement 2: The clinician should know that most patients with AD have increased serum IgE levels, which correlate with clinical measures of disease severity. (C)

Summary Statement 3: In determining treatments, the clinician should be aware that acute skin lesions of AD have a complex mixture of inflammatory cytokines that typically include T_H2 cells producing IL-4, IL-5, and IL-13 and T_H22 cells producing IL-22, although T_H1 cells expressing IFN-γ are also found in more chronic lesions. (C)

Summary Statement 4: The clinician should know that AD has become widely accepted as a disorder that is at least in part initiated by skin barrier defects. These barrier defects can be acquired or genetic. Murine models of AD strongly suggest that these barrier defects promote an adaptive immune response to epicutaneously applied antigens.

Summary Statement 5: The clinician should know that an inadequate innate immune response to epicutaneous microbes is in part responsible for susceptibility to infections and colonization with *Staphylococcus aureus*, as well as a number of viruses, in patients with AD. (C)

Summary Statement 6: When treating patients with AD, the clinician should remember that AD is a complex human disorder caused by the interaction of numerous susceptibility genes with the microenvironment (eg, tissue inflammation) and macroenvironment of the host. (B)

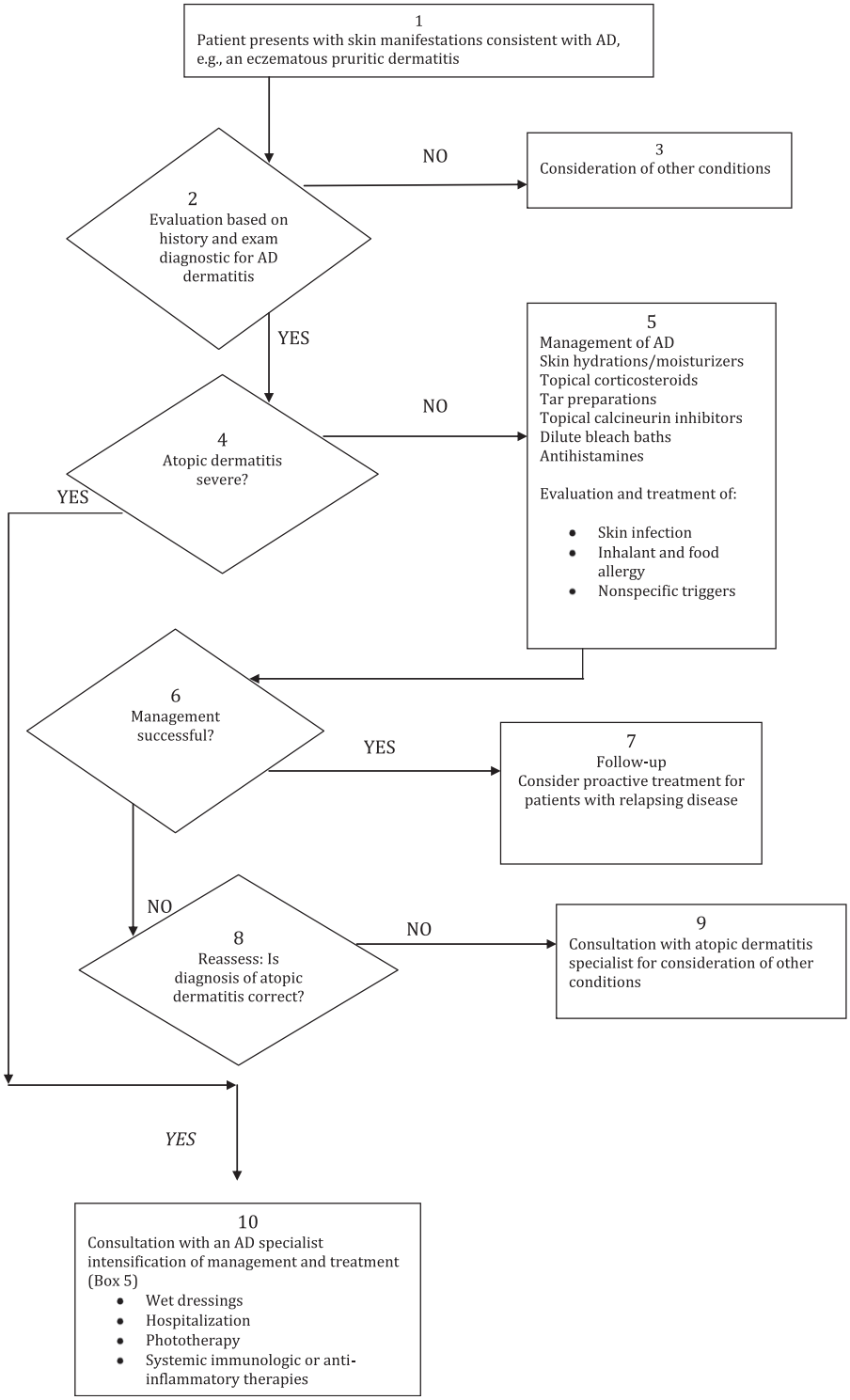

FIG 1. Flow chart of the diagnosis and management of AD (see the annotations for Fig 1 at the end of the complete document in this article's Online Repository at www.jacionline.org).

Clinical diagnosis

Summary Statement 7: The clinician should make the diagnosis of AD based on a constellation of clinical features. Pruritus and chronic or relapsing eczematous lesions with typical morphology and distribution in patients with a history of atopy are essential for diagnosis. (C)

Summary Statement 8: The physical examination findings seen by the clinician include acute and subacute skin lesions, which are most often seen in infants and young children and are characterized by intensely pruritic, erythematous papulovesicular lesions associated with excoriation and serous exudate. (D). Chronic AD is characterized by lichenification, papules, and excoriations. (D)

First-line management and treatment

Summary Statement 9: The intensity of management and treatment of AD is dictated by the severity of illness, which relates to the effect of AD on the quality of life of the patient and his or her family. (A)

Summary Statement 10: The clinician should establish treatment goals with the patient. These can include reduction in number and severity of flares and increase in disease-free periods. (D)

Summary Statement 11: Clinicians should use a systematic, multipronged approach that includes skin hydration, topical anti-inflammatory medications, antipruritic therapy, antibacterial measures, and elimination of exacerbating factors. Clinicians should evaluate the success of the approach and modify the treatment plan, if needed. (A)

Skin hydration. Summary Statement 12: The clinician should be aware that AD is characterized by reduced skin barrier function, which leads to enhanced water loss and dry skin; therefore the clinician should recommend hydration with warm soaking baths for at least 10 minutes followed by the application of a moisturizer. (D)

Summary Statement 13: Moisturizers should be recommended as first-line therapy. (D)

Topical corticosteroids. Summary Statement 14: If AD is not controlled by moisturizers alone, then the clinician should recommend a topical corticosteroid. (A)

Summary Statement 15: Low-potency corticosteroids are recommended for maintenance therapy, whereas intermediate- and high-potency corticosteroids should be used for the treatment of clinical exacerbation over short periods of time. (A)

Summary Statement 16: Clinicians should not prescribe potent fluorinated corticosteroids for use on the face, eyelids, genitalia, and intertriginous areas or in young infants. (D)

Summary Statement 17: Clinicians should recommend ultrahigh-potency corticosteroids only for very short periods (1-2 weeks) and in nonfacial nonskinfold areas. (D)

Summary Statement 18: When prescribing topical steroids, clinicians should remember that the degree of corticosteroid absorption through the skin and hence the potential for systemic adverse effects are directly dependent on the surface area of the skin involved, thickness of the skin, the use of occlusive dressing, and the potency of the corticosteroid preparation. (D)

Topical calcineurin inhibitors. *Topical tacrolimus.* Summary Statement 19: Clinicians can consider the use of tacrolimus ointment, which has been shown to be effective and safe in both adults and children older than 2 years for the treatment of AD, with most patients experiencing a reduction of pruritus within 3 days of initiating therapy. (A)

Summary Statement 20: Clinicians should consider the use of tacrolimus ointment, which, unlike topical steroids, does not cause atrophy for eczema on the face, eyelid, and skin folds that is unresponsive to low-potency topical steroids. (A)

Summary Statement 21: Clinicians must counsel patients that transient localized burning and itching can occur during the first week of topical tacrolimus. This might limit its usefulness in certain patients. (A)

Summary Statement 22: Once a flare is controlled, the clinician might consider prescribing tacrolimus ointment twice daily, twice weekly to eczema-prone areas to prevent future flares. (A)

Topical pimecrolimus. Summary Statement 23: Clinicians should consider the use of topical pimecrolimus cream, which is a calcineurin inhibitor that safely decreases the number of flares, reduces the need for corticosteroids, does not cause skin atrophy, and controls pruritus. (A)

Tar preparations. Summary Statement 24: Although tar preparations are widely used in the treatment of AD, there are no randomized controlled studies that have demonstrated their efficacy. (A)

Summary Statement 25: Newer coal tar products have been developed that are more cosmetically acceptable, with respect to odor and staining of clothes, than some older products. (B)

Summary Statement 26: Clinicians should not recommend tar preparations for acutely inflamed skin because this might result in additional skin irritation. (D)

Antihistamines. Summary Statement 27: Some patients might benefit from the use of antihistamines for the relief of pruritus associated with AD. (C)

Summary Statement 28: Treatment of AD with topical antihistamines is generally not recommended because of potential cutaneous sensitization. (C)

Vitamin D. Summary Statement 29: Patients with AD might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake. (B)

Dilute bleach baths. Summary Statement 30: Clinicians should consider the addition of dilute bleach baths twice weekly to reduce the severity of AD, especially in patients with recurrent skin infections. (A)

Identification and elimination of triggering factors

Summary Statement 31: The clinician should recommend avoidance of common irritants (eg, soaps, toiletries, wool, and chemicals) that trigger the itch-scratch cycle. (B)

Summary Statement 32: The clinician might consider recommending control of temperature and humidity to avoid increased pruritus related to heat, humidity, and perspiration. (D)

Summary Statement 33: Possible triggers of AD can be confirmed by using skin tests and *in vitro* tests for specific IgE antibodies and in some cases by using patch tests, which can produce immediate or delayed reactions to protein allergens. The clinician should only test for relevant allergens because testing, especially for foods, has low specificity. (B)

Summary Statement 34: The clinician might consider food allergens as triggers of AD more commonly in young infants and children. (D) The clinician should be aware that for children less than 5 years of age with moderate-to-severe AD, the Food Allergy Expert Panel suggested consideration of limited food allergy testing if the child has persistent AD in spite of optimized management and topical therapy, the child has a reliable history of an immediate allergic reaction after ingestion of the food, or both.

Summary Statement 35: The clinician should not recommend extensive elimination diets based only on positive skin or specific IgE test results because potential nutritional deficiency can occur, and even with multiple positive skin test results, most patients will react to few foods on oral challenge. (B)

Summary Statement 36: Aeroallergens, such as house dust mites, animal allergens, and pollens, can cause exacerbation, and therefore exposure to them should be minimized. (A)

Microbes

Summary Statement 37: The clinician should be aware that skin infections with *Staphylococcus aureus* are a recurrent problem in patients with AD, and patients with moderate-to-severe AD have been found to make IgE antibodies against staphylococcal toxins present in their skin. (B)

Summary Statement 38: The clinician should prescribe a short course of an appropriate systemic antibiotic only for patients who are clinically infected with *S aureus*. In areas with high levels of methicillin-resistant *S aureus*, the clinician might want to obtain a skin culture and initiate treatment with clindamycin, doxycycline, or trimethoprim-sulfamethoxazole while awaiting culture results. (A)

Summary Statement 39: AD can be complicated by recurrent viral skin infections, such as herpes simplex, warts, and molluscum contagiosum. The clinician should diagnose and promptly treat disseminated herpes simplex or eczema herpeticum with systemic antiviral agents. (B)

Summary Statement 40: The clinician should not immunize patients with AD or their household contacts with smallpox vaccination because they can have a severe, widespread, potentially fatal cutaneous infection called eczema vaccinatum, which is similar in appearance to eczema herpeticum. (C)

Summary Statement 41: The clinician should consider fungal infections that can complicate AD and might contribute to exacerbations. The diagnosis of dermatophytes can be made by using KOH preparation or culture. *Malassezia* species, which is a particular problem in young adults with refractory head and neck eczema, can be diagnosed clinically or with a KOH preparation. Specific IgE to *Malassezia* species might also be obtained. (C)

Quality of life and emotional stress

Summary Statement 42: The clinician should recognize that AD has a significant effect on patient and family quality of life and that patients have an increased risk for psychological distress. The clinician should ask about stress and emotional factors, which can cause exacerbations and have been found to induce immune activation, as well as to trigger pruritus and scratching. (C)

Summary Statement 43: The clinician should assess for sleep disturbances. Sleep might improve with treatment of inflammation, but the clinician might also consider therapeutic agents or referral to a sleep specialist or psychologist in severe cases or when sleep does not improve in remission. (C)

Patient education

Summary Statement 44: To achieve effective control of AD, the clinician should educate patients and family members about the chronic nature of the disease, exacerbating factors, and the safety/side effects of the medications. The clinician should also provide demonstrations of skin-care techniques, written treatment plans, and information about patient support organizations. (D)

Treatment of the difficult-to-manage patient

Consultation with an AD specialist. Summary Statement 45: The clinician should refer patients refractory to first-line therapy to an AD specialist. (D)

Wet dressings. Summary Statement 46: The clinician should recommend application of wet-wrap dressings in combination with topical corticosteroids for treatment of refractory AD. (A) Wet dressings help with skin barrier recovery, increase the efficacy of topical steroids when used concomitantly, and protect the skin from persistent scratching, allowing more rapid healing of excoriated lesions. (B)

Systemic immunomodulating agents. Summary Statement 47: Immunomodulating agents, such as cyclosporine, mycophenolate mofetil, azathioprine, IFN-γ, and corticosteroids, have been shown to provide benefit for patients with severe refractory AD, although the clinician should consider their potential serious adverse effects. (A)

Phototherapy. Summary Statement 48: UV therapy can be a useful treatment for recalcitrant AD. The most effective phototherapy option that is available in the United States is narrowband UVB. (A) The clinician should consider referral to a center with phototherapy availability.

Hospitalization. Summary Statement 49: The clinician might consider hospitalization, which can result in an improvement in AD by removing the patient from environmental allergens, irritants, and stressors and by providing patient/caregiver education, addressing sleep disturbance and psychosocial issues, intensifying treatment, and improving adherence with the treatment regimen. (D)

Allergen immunotherapy. Summary Statement 50: On the basis of several studies of dust mite immunotherapy, the clinician might consider allergen immunotherapy in selected patients with AD with aeroallergen sensitivity. (B)

Investigative approaches. Summary Statement 51: There are investigative treatments (intravenous immunoglobulin, omalizumab, and rituximab) that have been proposed for the management of AD. We do not recommend using them because they remain unproved at this time.

The summary statements with their supporting text are available online at www.jacionline.org.

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The Joint Task Force has made a concerted effort to acknowledge all contributors to this parameter. If any contributors have been excluded inadvertently, the Task Force will ensure that appropriate recognition of such contributions is made subsequently.

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CLASSIFICATION OF RECOMMENDATIONS AND EVIDENCE

Category of evidence

Ia Evidence from meta-analysis of randomized controlled trials
Ib Evidence from at least 1 randomized controlled trial
IIa Evidence from at least 1 controlled study without randomization
IIb Evidence from at least 1 other type of quasiexperimental study
III Evidence from nonexperimental descriptive studies, such as comparative studies
IV Evidence from expert committee reports, opinions or clinical experience of respected authorities or both

Strength of recommendation

A Directly based on category I evidence
B Directly based on category II evidence or extrapolated recommendation from category I evidence
C Directly based on category III evidence or extrapolated recommendation from category I or II evidence

D Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence
LB Laboratory based
NR Not rated

RESOLUTION OF NONDISQUALIFYING INTERESTS

The Joint Task Force recognizes that experts in a field are likely to have interests that could come into conflict with the development of a completely unbiased and objective practice parameter. A process has been developed to prevent potential conflicts from influencing the final document in a negative way to take advantage of that expertise.

At the workgroup level, members who have a potential conflict of interest either do not participate in discussions concerning topics related to the potential conflict, or if they do write a section on that topic, the workgroup completely rewrites it without their involvement to remove potential bias. In addition, the entire document is reviewed by the Joint Task Force, and any apparent bias is removed at that level. Finally, the practice parameter is sent for review both by invited reviewers and by anyone with an interest in the topic by posting the document on the Web sites of the ACAAI and the AAAAI.

HOW THIS PRACTICE PARAMETER WAS DEVELOPED

The Joint Task Force on Practice Parameters

The Joint Task Force on Practice Parameters is a 13-member taskforce consisting of 6 representatives assigned by the AAAAI, 6 assigned by the ACAAI, and 1 assigned by the Joint Council of Allergy & Immunology. This taskforce oversees the development of practice parameters, selects the workgroup chair or chairs, and reviews drafts of the parameters for accuracy, practicality, and clarity, as well as the broad utility of the recommendations for clinical practice.

The Atopic Dermatitis Practice Parameter workgroup

The Atopic Dermatitis Practice Parameters workgroup was commissioned by the Joint Task Force on Practice Parameters to update the previous practice parameters on atopic dermatitis. The Chair (Lynda Schneider, MD) invited workgroup members to participate in the parameter development who are considered to be experts in the field of atopic dermatitis. Workgroup members have been vetted for financial conflicts of interest by the Joint Task Force on Practice Parameters, and their conflicts of interest have been listed in this document and are posted on the Joint Task Force on Practice Parameters Web site at http://www.allergyparameters.org.

The charge to the workgroup was to use a systematic literature review in conjunction with consensus expert opinion to revise the 2004 Parameter on Atopic Dermatitis.

Protocol for finding evidence

A search of the medical literature was performed for a variety of terms that were considered relevant to this practice parameter. Literature searches were performed on PubMed and the Cochrane Database of Systematic Reviews. All reference types were included in the results. References identified as being relevant were searched for relevant references, and those references also were searched for relevant references. In addition, members of the workgroup were asked for references that were missed by this initial search. The timeframe searched was from January 2003 to June 2012. Although the ideal reference would consist of a randomized, double-blind, placebo-controlled study, the topics covered in this practice parameter were covered by relatively few such studies. Consequently, it was necessary to draw on a number of basic laboratory reports and observational studies to develop a complete document.

Glossary terms for search included *atopic dermatitis/atopic eczema* and *pathogenesis*, *genetics*, *diagnosis*, *management*, *therapy*, *triggers*, *staphylococcus*, *quality of life*, *sleep*, *cyclosporine*, *immunomodulating agents*, *phototherapy*, or *allergen immunotherapy.*

PREFACE

Atopic dermatitis (AD) is often the first manifestation of allergic disease. Most patients with AD will also have another atopic disorder, such as allergic rhinitis, asthma, or food allergy. Therefore the evaluation and management of AD are an integral part of an allergist/immunologist's training and practice. It is also important for the primary care physician to understand the basis for effective evaluation and management of patients with this condition because AD affects more than 10% of children and can have a significant effect on quality of life for the patient and the family unit. As discussed in this document, it is also important for the primary care physician to know when to appropriately consult an AD specialist.

Since the last parameter on AD was published in 2004, there have been remarkable advances in the understanding of the genetics and pathophysiology of the disease.[1] Hypotheses on the cause of AD must now include epidermal barrier defects, as well as immune dysregulation of both the innate and adaptive immune systems. AD is a complex inflammatory process, our understanding of which is constantly undergoing revision as more data become available on the role of IgE-bearing Langerhans cells, atopic keratinocytes, monocytes/macrophages, eosinophils, and mast cells and their interaction with IL-4–, IL-5–, and IL-13–producing T_H2, regulatory T, and T_H22 lymphocytes. There is a complicated interaction between these cells and their products and susceptibility genes and the host environment, which leads to the clinical findings that characterize AD.

The major objective of this parameter is to improve the care of patients with AD. This should be accomplished by establishing boundaries for the evaluation and management of patients with this condition while reducing unwanted and unnecessary variation in treatment.

This updated parameter was developed by the Joint Task Force on Practice Parameters, which has published 33 practice parameters for the field of allergy/immunology, including the original parameter on AD. The current document builds on the 2004 parameter on AD. It was written and reviewed by subspecialists in allergy and immunology, as well as dermatology, and was supported by the 3 allergy and immunology organizations noted above. Therefore this document represents an evidence-based, broadly accepted consensus opinion.

The major decision points in the evaluation and management of AD are noted in Fig E1 and explained in the Annotations. Also included in this parameter are summary statements, which represent the key points in the evaluation and management of AD. These summary statements appear again before each section in this document, followed by text that supports the summary statement or statements. There are sections on definitions, immunopathology and genetics, clinical diagnosis, first-line management and treatment, identification and elimination of triggering factors, microbes, emotional stress, patient education, and treatment of the difficult-to-manage patient.

EXECUTIVE SUMMARY

AD is a genetically transmitted, chronic inflammatory skin disease that affects 10% to 20% of children and 1% to 3% of adults.[2,3] In the vast majority of patients, the disease develops before the age of 5 years, although it develops in adulthood in as many as 20% of patients.[4] AD is the first manifestation of atopy in many patients who later have allergic rhinitis, asthma, or both, a pattern that has been referred to epidemiologically as "the atopic march." Pruritus, scratching, and chronic, relapsing, or both eczematous lesions are major hallmarks of the disease. In infants and young children, there is a characteristic pattern of involvement of the face, neck, and extensor skin surfaces. In older children and adults, the skin lesions often involve lichenification and are usually localized to the flexural folds of the extremities. Factors that can exacerbate symptoms in patients with AD include temperature, humidity, irritants, infections, food, inhalant and contact allergens, and emotional stress. Food allergy has been implicated in approximately one third of children with AD, although specific IgE might be present (eg, food sensitization) without clinical features of food allergy.[5]

The diagnosis of AD is based on its clinical presentation rather than the results of diagnostic testing.[6,7] However, the judicious use of percutaneous skin tests or *in vitro* tests for the presence of specific IgE to relevant allergens is a sensitive way of identifying potential allergic triggering factors. Double-blind food challenges are often necessary to determine the relevance of specific food ingestion to symptoms.[8] The effective management of AD involves a combination of trigger avoidance, measures to restore skin barrier function, and anti-inflammatory medication. Trigger avoidance should be individualized based on a careful history and the results of specific IgE testing. Barrier function can be improved by careful hydration and moisturizer application, such as soaking in a warm bath for at least 10 minutes followed by the immediate application of a moisturizer.

There are multiple anti-inflammatory medication options available for treating AD.[9,10] Topical corticosteroids are appropriate for the vast majority of patients, and the potency of the corticosteroid chosen should be individualized based on the severity of the dermatitis, the location of the affected skin, the surface area of the affected skin, and the age of the patient.[11] Clinical exacerbations might require temporarily switching to a more potent topical agent for a short period of time. Topical tacrolimus and pimecrolimus are anti-inflammatory calcineurin inhibitors and second-line agents that have been approved for topical use in adults and children (≥2 years of age) with AD.[12-14] These agents interrupt activation of lymphocytes and other inflammatory cells, and they have become an integral part of treating AD.[15-17]

There are a variety of other treatment options for patients with severe or refractory AD. These include wet dressings and occlusion[18-20]; phototherapy[21,22]; systemically administered immunosuppressants, such as cyclosporine[23]; and antimetabolites.[24,25] In rare cases short-term hospitalization might be a useful way to temporarily reduce exposure to environmental and emotional triggers while initiating intensive patient education, diagnostic testing (eg, skin testing and food challenges), intravenous antibiotics (if indicated), and aggressive topical treatment.

SUMMARY STATEMENTS

Definitions

Summary Statement 1: AD is a familial, chronic inflammatory skin disease that commonly presents during early infancy and childhood but can persist or start in adulthood. (C)

Immunopathology and genetics

Summary Statement 2: The clinician should know that most patients with AD have increased serum IgE levels, which correlate with clinical measures of disease severity. (C)

Summary Statement 3: In determining treatments, the clinician should be aware that acute skin lesions of AD have a complex mixture of inflammatory cytokines that typically include T_H2 cells producing IL-4, IL-5, and IL-13 and T_H22 cells producing IL-22, although T_H1 cells expressing IFN-γ are also found in more chronic lesions. (C)

Summary Statement 4: The clinician should know that AD has become widely accepted as a disorder that is at least in part initiated by skin barrier defects. These barrier defects can be acquired or genetic. Murine models of AD strongly suggest that these barrier defects promote an adaptive immune response to epicutaneously applied antigens.

Summary Statement 5: The clinician should know that an inadequate innate immune response to epicutaneous microbes is in part responsible for susceptibility to infections and colonization with *Staphylococcus aureus*, as well as a number of viruses, in patients with AD. (C)

Summary Statement 6: When treating patients with AD, the clinician should remember that AD is a complex human disorder caused by the interaction of numerous susceptibility genes with the microenvironment (eg, tissue inflammation) and macroenvironment of the host. (B)

Clinical diagnosis

Summary Statement 7: The clinician should make the diagnosis of AD based on a constellation of clinical features. Pruritus and chronic or relapsing eczematous lesions with typical morphology and distribution in patients with a history of atopy are essential for diagnosis. (C)

Summary Statement 8: The physical examination findings seen by the clinician include acute and subacute skin lesions, which are most often seen in infants and young children and are characterized by intensely pruritic, erythematous papulovesicular lesions associated with excoriation and serous exudate. (D). Chronic AD is characterized by lichenification, papules, and excoriations. (D)

First-line management and treatment

Summary Statement 9: The intensity of management and treatment of AD is dictated by the severity of illness, which relates

to the effect of AD on the quality of life of the patient and his or her family. (A)

Summary Statement 10: The clinician should establish treatment goals with the patient. These can include reduction in number and severity of flares and increase in disease-free periods. (D)

Summary Statement 11: Clinicians should use a systematic, multipronged approach that includes skin hydration, topical anti-inflammatory medications, antipruritic therapy, antibacterial measures, and elimination of exacerbating factors. Clinicians should evaluate the success of the approach and modify the treatment plan, if needed. (A)

Skin hydration. Summary Statement 12: The clinician should be aware that AD is characterized by reduced skin barrier function, which leads to enhanced water loss and dry skin; therefore the clinician should recommend hydration with warm soaking baths for at least 10 minutes followed by the application of a moisturizer. (D)

Summary Statement 13: Moisturizers should be recommended as first-line therapy. (D)

Topical corticosteroids. Summary Statement 14: If AD is not controlled by moisturizers alone, then the clinician should recommend a topical corticosteroid. (A)

Summary Statement 15: Low-potency corticosteroids are recommended for maintenance therapy, whereas intermediate- and high-potency corticosteroids should be used for the treatment of clinical exacerbation over short periods of time. (A)

Summary Statement 16: Clinicians should not prescribe potent fluorinated corticosteroids for use on the face, eyelids, genitalia, and intertriginous areas or in young infants. (D)

Summary Statement 17: Clinicians should recommend ultrahigh-potency corticosteroids only for very short periods (1-2 weeks) and in nonfacial nonskinfold areas. (D)

Summary Statement 18: When prescribing topical steroids, clinicians should remember that the degree of corticosteroid absorption through the skin and hence the potential for systemic adverse effects are directly dependent on the surface area of the skin involved, thickness of the skin, the use of occlusive dressing, and the potency of the corticosteroid preparation. (D)

Topical calcineurin inhibitors. *Topical tacrolimus.* Summary Statement 19: Clinicians can consider the use of tacrolimus ointment, which has been shown to be effective and safe in both adults and children older than 2 years for the treatment of AD, with most patients experiencing a reduction of pruritus within 3 days of initiating therapy. (A)

Summary Statement 20: Clinicians should consider the use of tacrolimus ointment, which, unlike topical steroids, does not cause atrophy for eczema on the face, eyelid, and skin folds that is unresponsive to low-potency topical steroids. (A)

Summary Statement 21: Clinicians must counsel patients that transient localized burning and itching can occur during the first week of topical tacrolimus. This might limit its usefulness in certain patients. (A)

Summary Statement 22: Once a flare is controlled, the clinician might consider prescribing tacrolimus ointment twice daily, twice weekly to eczema-prone areas to prevent future flares. (A)

Topical pimecrolimus. Summary Statement 23: Clinicians should consider the use of topical pimecrolimus cream, which is a calcineurin inhibitor that safely decreases the number of flares, reduces the need for corticosteroids, does not cause skin atrophy, and controls pruritus. (A)

Tar preparations. Summary Statement 24: Although tar preparations are widely used in the treatment of AD, there are no randomized controlled studies that have demonstrated their efficacy. (A)

Summary Statement 25: Newer coal tar products have been developed that are more cosmetically acceptable, with respect to odor and staining of clothes, than some older products. (B)

Summary Statement 26: Clinicians should not recommend tar preparations for acutely inflamed skin because this might result in additional skin irritation. (D)

Antihistamines. Summary Statement 27: Some patients might benefit from the use of antihistamines for the relief of pruritus associated with AD. (C)

Summary Statement 28: Treatment of AD with topical antihistamines is generally not recommended because of potential cutaneous sensitization. (C)

Vitamin D. Summary Statement 29: Patients with AD might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake. (B)

Dilute bleach baths. Summary Statement 30: Clinicians should consider the addition of dilute bleach baths twice weekly to reduce the severity of AD, especially in patients with recurrent skin infections. (A)

Identification and elimination of triggering factors

Summary Statement 31: The clinician should recommend avoidance of common irritants (eg, soaps, toiletries, wool, and chemicals) that trigger the itch-scratch cycle. (B)

Summary Statement 32: The clinician might consider recommending control of temperature and humidity to avoid increased pruritus related to heat, humidity, and perspiration. (D)

Summary Statement 33: Possible triggers of AD can be confirmed by using skin tests and *in vitro* tests for specific IgE antibodies and in some cases by using patch tests, which can produce immediate or delayed reactions to protein allergens. The clinician should only test for relevant allergens because testing, especially for foods, has low specificity. (B)

Summary Statement 34: The clinician might consider food allergens as triggers of AD more commonly in young infants and children. (D) The clinician should be aware that for children less than 5 years of age with moderate-to-severe AD, the Food Allergy Expert Panel suggested consideration of limited food allergy testing if the child has persistent AD in spite of optimized management and topical therapy, the child has a reliable history of an immediate allergic reaction after ingestion of the food, or both.

Summary Statement 35: The clinician should not recommend extensive elimination diets based only on positive skin or specific IgE test results because potential nutritional deficiency can occur, and even with multiple positive skin test results, most patients will react to few foods on oral challenge. (B)

Summary Statement 36: Aeroallergens, such as house dust mites, animal allergens, and pollens, can cause exacerbation, and therefore exposure to them should be minimized. (A)

Microbes

Summary Statement 37: The clinician should be aware that skin infections with *Staphylococcus aureus* are a recurrent

problem in patients with AD, and patients with moderate-to-severe AD have been found to make IgE antibodies against staphylococcal toxins present in their skin. (B)

Summary Statement 38: The clinician should prescribe a short course of an appropriate systemic antibiotic only for patients who are clinically infected with *S aureus*. In areas with high levels of methicillin-resistant *S aureus*, the clinician might want to obtain a skin culture and initiate treatment with clindamycin, doxycycline, or trimethoprim-sulfamethoxazole while awaiting culture results. (A)

Summary Statement 39: AD can be complicated by recurrent viral skin infections, such as herpes simplex, warts, and molluscum contagiosum. The clinician should diagnose and promptly treat disseminated herpes simplex or eczema herpeticum with systemic antiviral agents. (B)

Summary Statement 40: The clinician should not immunize patients with AD or their household contacts with smallpox vaccination because they can have a severe, widespread, potentially fatal cutaneous infection called eczema vaccinatum, which is similar in appearance to eczema herpeticum. (C)

Summary Statement 41: The clinician should consider fungal infections that can complicate AD and might contribute to exacerbations. The diagnosis of dermatophytes can be made by using KOH preparation or culture. *Malassezia* species, which is a particular problem in young adults with refractory head and neck eczema, can be diagnosed clinically or with a KOH preparation. Specific IgE to *Malassezia* species might also be obtained. (C)

Quality of life and emotional stress

Summary Statement 42: The clinician should recognize that AD has a significant effect on patient and family quality of life and that patients have an increased risk for psychological distress. The clinician should ask about stress and emotional factors, which can cause exacerbations and have been found to induce immune activation, as well as to trigger pruritus and scratching. (C)

Summary Statement 43: The clinician should assess for sleep disturbances. Sleep might improve with treatment of inflammation, but the clinician might also consider therapeutic agents or referral to a sleep specialist or psychologist in severe cases or when sleep does not improve in remission. (C)

Patient education

Summary Statement 44: To achieve effective control of AD, the clinician should educate patients and family members about the chronic nature of the disease, exacerbating factors, and the safety/side effects of the medications. The clinician should also provide demonstrations of skin-care techniques, written treatment plans, and information about patient support organizations. (D)

Treatment of the difficult-to-manage patient

Consultation with an AD specialist. Summary Statement 45: The clinician should refer patients refractory to first-line therapy to an AD specialist. (D)

Wet dressings. Summary Statement 46: The clinician should recommend application of wet-wrap dressings in combination with topical corticosteroids for treatment of refractory AD. (A) Wet dressings help with skin barrier recovery, increase the efficacy of topical steroids when used concomitantly, and protect the skin from persistent scratching, allowing more rapid healing of excoriated lesions. (B)

Systemic immunomodulating agents. Summary Statement 47: Immunomodulating agents, such as cyclosporine, mycophenolate mofetil, azathioprine, IFN-γ, and corticosteroids, have been shown to provide benefit for patients with severe refractory AD, although the clinician should consider their potential serious adverse effects. (A)

Phototherapy. Summary Statement 48: UV therapy can be a useful treatment for recalcitrant AD. The most effective phototherapy option that is available in the United States is narrowband UVB. (A) The clinician should consider referral to a center with phototherapy availability.

Hospitalization. Summary Statement 49: The clinician might consider hospitalization, which can result in an improvement in AD by removing the patient from environmental allergens, irritants, and stressors and by providing patient/caregiver education, addressing sleep disturbance and psychosocial issues, intensifying treatment, and improving adherence with the treatment regimen. (D)

Allergen immunotherapy. Summary Statement 50: On the basis of several studies of dust mite immunotherapy, the clinician might consider allergen immunotherapy in selected patients with AD with aeroallergen sensitivity. (B)

Investigative approaches. Summary Statement 51: There are investigative treatments (intravenous immunoglobulin, omalizumab, and rituximab) that have been proposed for the management of AD. We do not recommend using them because they remain unproved at this time.

DEFINITIONS

Summary Statement 1: AD is a familial, chronic inflammatory skin disease that commonly presents during early infancy and childhood but can persist or start in adulthood. (C)

AD is a heritable, chronic inflammatory skin disease that commonly presents during early infancy and childhood but can persist or start in adulthood.[4] It often presents as the first step in the atopic march toward respiratory allergy. Recent interest in AD has been sparked by reports of its increasing prevalence and the significant adverse effect it can have on quality of life. AD is a major public health problem worldwide, with lifetime prevalence in children of 10% to 20%.[2,3] The prevalence of AD in adults is approximately 1% to 3%. Wide variations in prevalence have been observed within countries inhabited by similar ethnic groups, suggesting that environmental factors determine AD expression.[26]

IMMUNOPATHOLOGY AND GENETICS

Summary Statement 2: The clinician should know that most patients with AD have increased serum IgE levels, which correlate with clinical measures of disease severity. (C)

Summary Statement 3: In determining treatments, the clinician should be aware that acute skin lesions of AD have a complex mixture of inflammatory cytokines that typically include T_H2 cells producing IL-4, IL-5, and IL-13 and T_H22 cells producing IL22, although in more chronic lesions T_H1 cells expressing IFN-γ are also found. (C)

Summary Statement 4: The clinician should know that AD has become widely accepted as a disorder that is at least in part initiated by skin barrier defects. These barrier defects

can be acquired or genetic. Murine models of AD strongly suggest that these barrier defects promote an adaptive immune response to epicutaneously applied antigens.

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Summary Statement 6: When treating patients with AD, the clinician should remember that AD is a complex human disorder caused by the interaction of numerous susceptibility genes with the microenvironment (eg, tissue inflammation) and macroenvironment of the host. (B)

Since the last Joint Task Force practice parameter on atopic dermatitis was published,[27] there have been several key advances in our understanding of the pathophysiology of AD. Current hypotheses take into account epidermal barrier defects, the robust T_H2 response to antigens, and cutaneous innate immune defects. It is likely that the relative contribution of each of these defects and their interactions will help explain the remarkable heterogeneity we observe in the clinical presentation and course of our patients with AD.

Physiologic impairment of the skin barrier has long been recognized as a hallmark of AD. We now know that the outermost epidermal layer called the stratum corneum is dysfunctional in patients with AD as the result of 1 or more of the following defects: reduced levels of stratum corneum lipids; defects in proteases, antiproteases, or both; acquired or genetic defects in structural proteins, such as filaggrin, loricrin, and other epidermal differentiation complex genes[28]; and/or physical trauma from the itch-scratch cycle. In 2006, null mutations in the filaggrin gene *(FLG)* were strongly linked to AD and several subphenotypes (early-onset, severe/persistent, and eczema herpeticum).[28] Studies in filaggrin-deficient mice support the barrier theory by demonstrating that allergens or irritants applied on the skin surface resulted in enhanced reactions in comparison with those seen in wild-type mice.[29] The epidermis has an additional barrier structure called tight junctions, which are found just below the stratum corneum within the stratum granulosum. A defect in epidermal tight junction function has been observed in the skin of patients with AD, which is attributable in part to a reduction in claudin-1 (CLDN1) levels.[30] In summary, the leaky skin barrier is thought to promote greater immunologic responsiveness to allergens and irritants, 2 clinical hallmarks of AD.[28,30,31]

For several decades, we have known that there is an adaptive immune defect in patients with AD characterized by the increased frequency of T_H2 cells producing IL-4, IL-5, and IL-13 in the peripheral blood and acute skin lesions, whereas a more mixed T_H1 and T_H2 infiltrate is observed in chronic skin lesions.[32] T_H2 cytokines are largely responsible for the eosinophilia and IgE sensitization observed to a host of environmental antigens. This T_H2 polarity is thought to occur as a consequence of a number of factors, including the release of IL-25, IL-33, and thymic stromal lymphopoietin, which are released from barrier-disrupted epidermis or after general tissue damage.[29,33-36] The release of these pro-T_H2 mediators by epidermal cells develops in response to allergen actions either on innate immune receptors or through proteolytic actions of the allergen itself. These mediators activate resident antigen-presenting cells, including basophils and dendritic cells, which promote T_H2 development at the draining lymph node.[37] Interestingly, several epidermal barrier defects (eg, reduced filaggrin, claudin-1, and lymphoepithelial Kazal-type 5 serine protease inhibitor [LEKTI] levels) observed in patients with AD correlate inversely with markers of T_H2 polarity.[28,30,38] A considerable amount of evidence suggests that T_H2 cytokines are associated with and in part responsible for the increased frequency and greater severity of bacterial and viral skin infections observed in this population.[39,40] For example, T_H2 cytokines dampen several components of the innate and adaptive immune system required for an effective host defense, and they reduce the expression of barrier proteins in the epidermal differentiation complex, such as filaggrin, involucrin, loricrin, and S100 proteins.[31] Recently, several groups have observed increased expression of IL-22 within AD skin lesions. This cytokine is released from both T_H17 cells and from a newly recognized CD4 memory T-cell population called T_H22 cells, which were first identified in patients with AD.[31,41,42] IL-22 induces epithelial proliferation, which might explain the thickened epidermis observed in AD lesions.[43] Whether T_H17 cells play a key role in human AD is still unclear.[44-46]

There is mounting evidence that defects in the innate immune system play a role in the susceptibility of patients with AD to cutaneous microbes and that these defects might affect the magnitude and character of the adaptive immune response to allergens. Unique motifs expressed on microbes or molecules released in response to tissue injury trigger inflammatory responses from pattern-recognition receptors, such as the Toll-like receptor family. For example, patients with AD have reduced expression, function, or both of Toll-like receptor 2 on their epidermal cells and monocytes, which might in part be genetically determined.[47] In addition, their keratinocytes have a reduced capacity to produce broad-spectrum antimicrobial peptides called defensins and cathelicidins, which act as natural antibiotics to kill a wide variety of bacterial, viral, and fungal pathogens. They also have reduced recruitment of innate immune cells (eg, PMNs, plasmacytoid dendritic cells, and natural killer cells) to sites of skin inflammation. All of these findings are credible explanations for the susceptibility of patients with AD to pathogens, such as *S aureus*, herpes simplex virus, and vaccinia virus.

AD is a human disorder that develops as a consequence of complex interactions between susceptibility genes and environmental exposures. Family histories have long identified a strong genetic component to this disease. More than 80 genes have been implicated in genetic studies by using candidate gene approaches and genome-wide association studies, and most of the implicated genes are either relevant for the development of a T_H2 immune response, innate immune responses, or an intact epidermal barrier. To date, mutations in the stratum corneum gene *FLG* confer the greatest risk for AD and have been replicated in many AD populations and AD subphenotypes (eg, AD with asthma, AD with a history of eczema herpeticum, persistent AD, and early-onset AD).[48] Genome-wide association studies suggest that other epidermal differentiation genes will likely be identified in the locus around chromosome 1q21. It is interesting to note that the expression of a number of proteins important for the formation of the cornified envelope, including filaggrin, loricrin, and involucrin, are reduced by T_H2 cytokines characteristically present in acute AD lesions. Therefore some of the barrier defects observed in patients with AD might develop on an acquired basis because of local tissue factors.

Our current approach to the treatment of AD has focused on identifying and minimizing allergen exposure and reducing tissue

inflammation. With the recognition that this is a disease mediated, at least in part, by epidermal barrier disruption, as well as the release of potent tissue-derived adjuvants and cutaneous innate immune defects, we are likely to see therapies developed that begin to address these other defects. We hope this multipronged approach will provide greater relief for our patients than our current treatments have been able to achieve.

CLINICAL DIAGNOSIS

Summary Statement 7: The clinician should make the diagnosis of AD based on a constellation of clinical features. Pruritus and chronic or relapsing eczematous lesions with typical morphology and distribution in patients with a history of atopy are essential for diagnosis. (C)

Summary Statement 8: The physical examination findings seen by the clinician include acute and subacute skin lesions, which are most often seen in infants and young children and are characterized by intensely pruritic, erythematous papulovesicular lesions associated with excoriation and serous exudate. (D). Chronic AD is characterized by lichenification, papules, and excoriations. (D)

At the initial encounter with any patient seeking treatment for AD, particularly if symptoms are poorly controlled, it is essential to confirm that the correct diagnosis has been made. There is no objective diagnostic test for the clinical confirmation of AD. Therefore the clinician should make the diagnosis of AD based on the constellation of clinical features and, by some criteria, the presence of allergen-specific IgE.[6,7,49,50] Although clearly playing a role in some portion of cases, filaggrin expression is not yet of diagnostic relevance.[51] Of the major features, pruritus and chronic or relapsing eczematous lesions with typical morphology and distribution are essential for diagnosis. Pruritus can occur throughout the day but is often worse in the early evening and night. Its consequences are scratching followed by the elicitation of eczematous skin lesions.

Acute and subacute skin lesions are characterized by intensely pruritic, erythematous papulovesicles associated with excoriation and serous exudate. Chronic AD is characterized by lichenification, papules, and excoriations. Patients usually have dry, pale, pasty skin. The distribution and skin reaction pattern vary according to the patient's age, disease activity, and accessibility to scratching. In infants and young children, the rash generally involves the face, neck, and extensor skin surfaces. In older children and adults who have long-standing skin disease, lichenification and localization of the rash to the flexural folds of the extremities are common. Chronic hand eczema might be the primary manifestation in many adults with a history of AD.

AD is often associated with an early age of onset, with most cases starting before the age of 5 years; however, AD can begin in adulthood. AD can be triggered by IgE-mediated events in some patients but also can be triggered by non–IgE-mediated events.[4,52] Therefore although respiratory and food allergies are important associated conditions in patients with AD, they are not essential for the diagnosis of this condition. Although a number of other features, such as Dennie-Morgan infraorbital folds, white dermatographism, or hyperlinear palms, can be seen and help the clinician in making a diagnosis, they are too nonspecific for use in defining AD for research studies.[6] A firm diagnosis of AD depends on the exclusion of other skin conditions that share symptoms and signs (see Annotation 3 in this article's Online Repository at www.jacionline.org for further discussion).

FIRST-LINE MANAGEMENT AND TREATMENT

Summary Statement 9: The intensity of management and treatment of AD is dictated by the severity of illness, which relates to the effect of AD on the quality of life of the patient and his or her family. (A)

Summary Statement 10: The clinician should establish treatment goals with the patient. These can include reduction in number and severity of flares and increase in disease-free periods. (D)

Summary Statement 11: Clinicians should use a systematic, multipronged approach that includes skin hydration, topical anti-inflammatory medications, antipruritic therapy, antibacterial measures, and elimination of exacerbating factors. Clinicians should evaluate the success of the approach and modify the treatment plan, if needed. (A)

The intensity of management and treatment is dictated by the severity of illness and its effect on the patient and his or her immediate family. Goals of therapy should be to reduce the number and severity of flares and to maximize disease-free periods, with no or minimal side effects of therapy. Successful management requires a systematic multipronged approach that includes skin hydration, topical anti-inflammatory medications, antibacterial measures, and elimination of exacerbating factors, including irritants, allergens, and emotional stressors.[11,16] Clinicians should evaluate the success of the approach and modify the treatment plan, if needed. Scratching plays a central role in the development of cutaneous lesions in patients with AD. Therefore control of pruritus is an important part of treatment, recognizing that patients might be exposed to both exogenous (eg, humidity and allergens) and endogenous (eg, stress) provocation factors. Dry skin in the winter months damages the stratum corneum barrier, causing an increased susceptibility to irritants and increased itching, whereas sweating in the warm humid months of the summer can also trigger itching. Patients with AD frequently will experience an accentuation of their itching during times of stress, exposure to specific allergens, or both. Many factors can lead to an intensification of pruritus, and treatment plans should be individualized to address trigger factors that are unique to the individual patient.

SKIN HYDRATION

Summary Statement 12: The clinician should be aware that AD is characterized by reduced skin barrier function, which leads to enhanced water loss and dry skin; therefore the clinician should recommend hydration with warm soaking baths for at least 10 minutes followed by the application of a moisturizer. (D)

Summary Statement 13: Moisturizers should be recommended as first-line therapy. (D)

AD is characterized by reduced skin barrier function. At least in part, this is likely because of high expression of sphingomyelin deacylase, which decreases ceramide levels in AD skin.[53,54] The loss of vital skin lipids results in enhanced transepidermal water loss and dry skin (xerosis). Application of ceramide-rich lipids might improve skin barrier function and reduce the severity of AD.[55] However, it is not clear that more expensive "barrier

creams" are more effective than traditional moisturizing agents, such as petrolatum.[56] Xerosis contributes to the development of epithelial microfissures and cracks, which allow entry of microbes and allergens. This problem usually becomes exacerbated during the dry winter months and is aggravated in certain work environments. Warm soaking baths for at least 10 minutes followed by the application of an occlusive moisturizer to retain moisture can provide the patient symptomatic relief.[57] Addition of substances, such as oatmeal or baking soda, to the bath water can have a soothing antipruritic effect for certain patients but does nothing to increase water absorption. Moisturizers make a major contribution to controlling the pruritus of patients with AD while maintaining a soft texture to the skin.[58] They offer a particular advantage when applied to dry skin and after bathing to maintain hydration of the epidermis.[59] Consistent use of moisturizers has a corticosteroid-sparing effect.[60-62] Moisturizers are available in the form of lotions, creams, and ointments. Lotions and creams can be irritating because of preservatives, solubilizers, and fragrances. Lotions can be drying because of an evaporative effect. Hydrophilic ointments can be obtained in varying degrees of viscosity. Some patients prefer a thicker preparation than others might require. Occlusive ointments are sometimes not well tolerated because of interference with the function of the eccrine sweat ducts and can induce the development of sweat retention dermatitis. In these patients less occlusive agents should be used. The science of moisturization is complex and incomplete; more studies are needed to understand the optimal approach.

TOPICAL CORTICOSTEROIDS

Summary Statement 14: If AD is not controlled by moisturizers alone, then the clinician should recommend a topical corticosteroid. (A)

Summary Statement 15: Low-potency corticosteroids are recommended for maintenance therapy, whereas intermediate and high-potency corticosteroids should be used for the treatment of clinical exacerbation over short periods of time. (A)

Summary Statement 16: Clinicians should not prescribe potent fluorinated corticosteroids for use on the face, eyelids, genitalia, and intertriginous areas or in young infants. (D)

Summary Statement 17: Clinicians should recommend ultrahigh-potency corticosteroids only for very short periods (1-2 weeks) and in nonfacial nonskinfold areas. (D)

Summary Statement 18: When prescribing topical steroids, clinicians should remember that the degree of corticosteroid absorption through the skin and hence the potential for systemic adverse effects are directly dependent on the surface area of the skin involved, thickness of the skin, the use of occlusive dressing, and the potency of the corticosteroid preparation. (D)

Corticosteroids are effective medications for the treatment of AD.[11] However, patients should be carefully instructed in their use to avoid potential adverse effects. Certain areas, including the mucous membranes (lips), genitalia, eyelids, face, and intertriginous areas, have increased potential for transepidermal corticosteroid penetration, and for this reason, potent fluorinated corticosteroids should be avoided in these areas. A low-potency corticosteroid preparation is generally recommended for these areas. For patients with very severe AD, clinicians might consider a few days of higher-potency topical steroids but should warn patients about local side effects and prescribe a limited amount of the topical steroid. Cheilitis can be problematic in patients with AD, and a few days of 1% or 2.5% hydrocortisone ointment (eg, CortiBalm; Dr. Dan's Lip Balms, Milan, Ind) followed by frequent use of moisturizers is usually effective.

Patients should be instructed to apply topical corticosteroids to skin lesions and to use moisturizers over uninvolved skin. There are 7 classes of topical corticosteroids ranked according to their potency based on vasoconstrictor assays. Some of the commonly used ones are listed in Table E1. Group I includes the super-potent topical corticosteroids with the greatest potential for adverse effects, both localized and systemic. Group VII includes the least potent topical corticosteroids and, as a group, has the least potential for adverse effects. More potent topical corticosteroids can be used for several days in nonfacial nonskinfold areas to treat acute rashes. Patients should then be instructed to reduce the potency of topical corticosteroids applied to the skin.

Because of their potential adverse effects, the ultrahigh-potency corticosteroids should be used for only very short periods of time (1-2 weeks) and not on facial or skinfold areas. The high-potency corticosteroids should only be used for short periods of time (up to 3 weeks) for clinical exacerbations. Intermediate-potency corticosteroids, such as 0.1% triamcinolone, can be used for longer periods of time to treat chronic AD involving the trunk and extremities. Corticosteroids in gel formulations can contain a propylene glycol base that can irritating to the skin, in addition to promoting dryness, limiting their use to the scalp and beard areas. In general, compared with topical creams, ointments have enhanced topical potency, although some modern vehicles might offset this tendency.[63]

Adverse effects from topical corticosteroids are directly related to the potency ranking of the compound and the duration of use. It is incumbent on the clinician to balance the need for therapeutic potency with the potential for adverse effects. Adverse effects from topical corticosteroids can be divided into local and systemic adverse effects. Systemic adverse effects, which occur rarely, include suppression of the hypothalamic-pituitary-adrenal axis. Local adverse effects include the development of striae and atrophy of the skin, perioral dermatitis, rosacea, and allergic contact dermatitis (caused by the vehicle or steroid itself). Systemic adverse effects are related to the potency of the topical corticosteroid, the site of application, the occlusiveness of the preparation, the percentage of the body covered, and the length of use. The potential for prolonged use of potent topical corticosteroids to cause adrenal suppression is greatest in small children and infants.[64,65]

Two newer topical corticosteroids (fluticasone propionate and mometasone furoate) appear to have less systemic absorption and an efficacy profile that allows them to be used once as opposed to twice daily.[66,67] Furthermore, several trials support that once control of AD is achieved with a daily regimen of topical corticosteroid, long-term control can be maintained with twice-weekly applications of topical fluticasone propionate to areas that have healed but are prone to eczema.[68,69,70]

TOPICAL CALCINEURIN INHIBITORS

Topical tacrolimus

Summary Statement 19: Clinicians can consider the use of tacrolimus ointment, which has been shown to be effective and

safe in both adults and children older than 2 years for the treatment of AD, with most patients experiencing a reduction of pruritus within 3 days of initiating therapy. (A)

Summary Statement 20: Clinicians should consider the use of tacrolimus ointment, which, unlike topical steroids, does not cause atrophy for eczema on the face, eyelid, and skin folds, for AD that is unresponsive to low-potency topical steroids. (A)

Summary Statement 21: Clinicians must counsel patients that transient localized burning and itching can occur during the first week of topical tacrolimus. This might limit its usefulness in certain patients. (A)

Summary Statement 22: Once a flare is controlled, the clinician might consider prescribing tacrolimus ointment twice daily, twice weekly to eczema-prone areas to prevent future flares. (A)

Tacrolimus is a drug that acts by binding with high affinity to a 12-kDa cytoplasmic macrophilin, and the complex inhibits the activity of calcineurin, a calcium-dependent phosphatase. This in turn inhibits the translocation of the transcription factor nuclear factor of activated T cells into the cell nucleus, blocking the initiation of nuclear factor of activated T cells–dependent gene transcription. Tacrolimus inhibits the activation of key cells involved in AD, including T cells, dendritic cells, mast cells, and keratinocytes.[71] Unlike cyclosporine, another well-known systemic calcineurin inhibitor, tacrolimus exhibits activity when applied topically. Multicenter, blinded, vehicle-controlled studies with tacrolimus ointment, both 0.03% and 0.1%, in both adults and children have reported topically applied tacrolimus to be effective and safe.[12,72-74] A local burning sensation is the only common adverse event. Most patients experience a reduction of this sensation within 3 days of initiating therapy. A small percentage of patients can experience increased likelihood of facial flushing after an alcoholic beverage. In adults a dose-response effect was seen between 0.03% and 0.1% tacrolimus, particularly for patients with more severe skin disease. Patients with AD treated with topical tacrolimus have been reported to have a significant improvement in quality of life.[75]

Tacrolimus ointment (Protopic; Astellas, Northbrook, Ill) 0.03% has been approved for short-term and intermittent long-term use in children 2 to 15 years of age with moderate-to-severe AD. It has also been approved in both the 0.03% and 0.1% concentrations for adults. Long-term open-label studies with tacrolimus ointment have been performed in adults and children, with sustained efficacy and no significant adverse effects.[76,77] In addition, unlike topical glucocorticoids, tacrolimus ointment is not atrophogenic and has a greater therapeutic margin of safety than medium-strength glucocorticosteroids for facial and eyelid eczema.

There is a group of patients with corticosteroid insensitivity who might benefit from early treatment with topical tacrolimus because corticosteroid-resistant T cells have been found to respond well to tacrolimus.[78] Furthermore, patients with recalcitrant facial eruptions resistant to topical corticosteroids have reported benefit from use of topical tacrolimus.[79]

A multicenter, randomized, double-blind, parallel-group study comparing 0.03% and 0.1% tacrolimus ointment with a mid-potency topical corticosteroid (hydrocortisone-17-butyrate) ointment was performed in 570 adults with moderate-to-severe AD.[80] This 3-week study demonstrated that a 0.1% concentration of tacrolimus had a similar efficacy as 0.1% hydrocortisone-17-butyrate. Another randomized, double-blind, parallel-group study compared 0.03% and 0.1% tacrolimus ointment with a low-potency topical corticosteroid (1% hydrocortisone acetate ointment) in 560 children 2 to 15 years old with moderate-to-severe AD.[81] Both 0.03% and 0.1% tacrolimus ointment were significantly more effective than 1% hydrocortisone acetate ointment in reducing skin inflammation caused by AD. These 2 studies suggest that 0.1% tacrolimus ointment has the strength of a mid-potency topical corticosteroid and should be considered first-line therapy for facial eczema where treatment with corticosteroids is limited to low-potency topical corticosteroids because of safety concerns.

Several recent studies support the use of tacrolimus as a twice-weekly maintenance therapy to eczema-prone areas, with good effect in reducing additional flares, similar to the fluticasone studies previously discussed.[14,70,82] Although not US Food and Drug Administration (FDA) approved for this indication in the United States, topical tacrolimus is approved for use in Europe as twice-weekly maintenance/proactive therapy to areas typically with AD in patients as young as 2 years of age for up to 12 months.

Concern has been raised regarding the potential effects of this new class of topical calcineurin inhibitors on the prevalence of local viral infections (eg, herpes simplex), and therefore patients should be monitored for this possible complication.[83-85] In contrast, the number of *S aureus* organisms on AD skin decreases with prolonged use of topical tacrolimus because of its effective control of skin inflammation.[86]

Topical pimecrolimus

Summary Statement 23: Clinicians should consider the use of topical pimecrolimus cream, which is a calcineurin inhibitor that safely decreases the number of flares, reduces the need for corticosteroids, does not cause skin atrophy, and controls pruritus. (A)

Pimecrolimus is an ascomycin macrolactam derivative that binds with high affinity to its cytosolic receptor, macrophilin-12, and thereby inhibits calcineurin by using a similar mechanism as tacrolimus. However, studies in experimental animals suggest that structural differences in lipophilicity endow pimecrolimus, as compared with tacrolimus, with the ability to preferentially distribute to the skin as opposed to the systemic circulation.[87] In clinical studies pimecrolimus blood levels have remained consistently low, with no clinically relevant drug-related systemic adverse events reported.[88] As a consequence of inhibiting calcineurin, pimecrolimus inhibits T-cell proliferation, prevents the gene transcription of T_H1 and T_H2 cytokines, and reduces mediator release from mast cells and basophils.[17] Topical application in human subjects has not been associated with the atrophy observed with topical corticosteroids.[89] However, a shared concern with tacrolimus is that pimecrolimus can increase the risk of viral infections, such as eczema herpeticum and molluscum contagiosum, in treated skin.[89]

Short-term, multicenter, blinded, vehicle-controlled studies with pimecrolimus cream 1% in patients with AD have shown pimecrolimus to be both effective and safe.[13] Significant relief of pruritus relative to the vehicle control was observed in the pimecrolimus-treated group at the first efficacy evaluation, 8 days after initial application of the study medication. Pimecrolimus cream 1% (Elidel; Novartis Pharmaceuticals, East Hanover, NJ) has been approved for short-term and intermittent long-term use in patients with mild-to-moderate AD who are 2 years and

older. Although not approved by the FDA for use in children less than 2 years of age, multiple studies have shown safety and efficacy in infants and young children.[90-96] When used as long-term maintenance therapy, topical pimecrolimus has been found to reduce the number of exacerbations caused by AD and to reduce the need for corticosteroid therapy.[91,97]

In 2006, the FDA issued a black-box warning on the topical calcineurin inhibitors because they were being prescribed as first-line therapy, and there was concern about potential carcinogenicity.[98] Prospective long-term studies are in progress for both topical tacrolimus and pimecrolimus. A nested case-control study of almost 300,000 patients with AD did not find an increased risk of lymphoma in patients treated with topical calcineurin inhibitors. Severity of AD was associated with an increased risk of lymphoma (odds ratio, 2.4; 95% CI, 1.5-3.8).[99]

Tar preparations

Summary Statement 24: Although tar preparations are widely used in the treatment of AD, there are no randomized controlled studies that have demonstrated their efficacy. (A)

Summary Statement 25: Newer coal tar products have been developed that are more cosmetically acceptable, with respect to odor and staining of clothes, than some older products. (B)

Summary Statement 26: Clinicians should not recommend tar preparations for acutely inflamed skin because this might result in additional skin irritation. (D)

Crude coal tar extracts were used to reduce skin inflammation before the availability of topical corticosteroids. However, the anti-inflammatory properties of tars are not well characterized. There are no well-controlled, randomized, vehicle-controlled studies with tar preparations.[11,100] Therefore part of the improvement observed with tar preparations could be due to a placebo effect that can be significant in patients with AD. Coal tar products have been developed that are more cosmetically acceptable, with respect to odor and staining of clothes, than some older products.[101] To increase compliance, tar preparations might be recommended at bedtime. The preparation is then removed by washing in the morning, thus eliminating concern about odor during the day and limiting staining of daytime clothing. Tar preparations should not be used on acutely inflamed skin because this can result in additional skin irritation. There is a theoretic risk of tar being a carcinogen based on observational studies of workers using tar components in their occupations. Recently, a sufficiently powered cohort analysis of both patients with psoriasis and those with eczema treated with tar found no increased risk of malignancies.[102] Adverse effects associated with tars include folliculitis and, occasionally, photosensitivity. Tar shampoos are often beneficial when AD involves the scalp.

Antihistamines

Summary Statement 27: Some patients might benefit from the use of antihistamines for the relief of pruritus associated with AD. (C)

Summary Statement 28: Treatment of AD with topical antihistamines is generally not recommended because of potential cutaneous sensitization. (C)

Oral antihistamines are commonly prescribed for control of pruritus in patients with AD. However, an evidence-based review of 16 controlled studies revealed little objective evidence demonstrating the relief of pruritus when sedating or nonsedating antihistamines were used in the treatment of AD.[103] A more recent trial showed no significant effect of chlorpheniramine on relieving itch in patients with AD.[104] Although the majority of these studies were flawed because of small sample size or poor study design, these observations are not surprising because histamine is only one of many mediators released during the inflammatory response that can induce pruritus. In fact, reduction of skin inflammation with topical glucocorticoids and calcineurin inhibitors will often reduce pruritus.[12,13,66,73]

However, these observations do not exclude the possibility that there are patients with AD who might benefit from the use of antihistamines, particularly those patients with concomitant urticaria or allergic rhinitis.[105] There has been some suggestion that second-generation antihistamines might be more effective in relieving symptoms of AD, but the largest trial to date did not demonstrate any overall benefit from cetirizine in children with AD.[106-110] Because pruritus is usually worse at night, sedating antihistamines (eg, hydroxyzine or diphenhydramine) offer an advantage when used at bedtime. If severe nocturnal pruritus persists, short-term use of a sedative to allow adequate rest might be appropriate. Treatment of AD with topical antihistamines is generally not recommended because of potential cutaneous sensitization.[111] However, a multicenter, double-blind, vehicle-controlled study of topical 5% doxepin cream demonstrated a significant reduction of pruritus.[112] In this 1-week study, sensitization was not reported. However, sedation can occur with widespread application, and irritation has also been noted by patients.

Vitamin D

Summary Statement 29: Patients with AD might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake. (B)

AD frequently worsens during the winter months. In a small study supplementation of patients who reported worsening of their eczema in the winter with vitamin D resulted in a significant improvement in 80% of the treated patients versus only 17% of the control group at 1 month.[113] A more recent study also found a significant effect with oral vitamin D supplementation in a study of 45 patients with AD compared with placebo.[114] Another group found a strong negative correlation between serum vitamin D levels and the severity of AD in children, providing another supportive line of evidence for supplementation of vitamin D.[115] Despite the relatively few studies, the robustness of the effect and the multiple lines of evidence suggest that systemic vitamin D supplementation might be of benefit, especially in those whose symptoms appear to worsen during the winter. However, topical vitamin D preparations are to be avoided because they might worsen eczematous dermatitis through both allergic and irritant mechanisms.[116,117]

Dilute bleach baths

Summary Statement 30: Clinicians should consider the addition of dilute bleach baths twice weekly to reduce the severity of AD, especially in patients with recurrent skin infections. (A)

Although 1 large meta-analysis of methods to reduce *S aureus* in patients with eczema did not show evidence for benefit, the role

of *S aureus* colonization is important both in terms of infection and immune stimulation.[118] Dilute sodium hypochlorite bleach baths have been suggested for many years and perhaps can be traced back to the use of Dakin solution for colonized or infected wounds during World War I. Intermittent soaking in a dilute bleach bath has been likened to swimming in a chlorinated swimming pool and might reduce the need for systemic antibiotics in heavily colonized patients.[119] In one randomized trial the group who received dilute bleach baths (one-half cup of bleach in 40 gallons of water) twice weekly plus intranasal mupirocin (5 days/month) had significantly decreased severity of AD at 1 and 3 months compared with placebo.[120] Further studies are needed to validate this technique, as well as to delineate the optimal frequency of the baths and the most appropriate eczema subtype, but dilute bleach baths can be an inexpensive and gentle therapy to consider.

IDENTIFICATION AND ELIMINATION OF TRIGGERING FACTORS

Summary Statement 31: The clinician should recommend avoidance of common irritants (eg, soaps, toiletries, wool, and chemicals) that trigger the itch-scratch cycle. (B)

Summary Statement 32: The clinician might consider recommending control of temperature and humidity to avoid increased pruritus related to heat, humidity, and perspiration. (D)

Summary Statement 33: Possible triggers of AD can be confirmed by using skin tests and *in vitro* tests for specific IgE antibodies and in some cases by using patch tests, which can produce immediate or delayed reactions to protein allergens. The clinician should only test for relevant allergens because testing, especially for foods, has low specificity. (B)

Summary Statement 34: The clinician might consider food allergens as triggers of AD more commonly in young infants and children. (D) The clinician should be aware that for children less than 5 years of age with moderate-to-severe AD, the Food Allergy Expert Panel suggested consideration of limited food allergy testing if the child has persistent AD in spite of optimized management and topical therapy, the child has a reliable history of an immediate allergic reaction after ingestion of the food, or both.

Summary Statement 35: The clinician should not recommend extensive elimination diets based only on positive skin or specific IgE test results because potential nutritional deficiency can occur and, even with multiple positive skin test results, most patients will react to few foods on oral challenge. (B)

Summary Statement 36: Aeroallergens, such as house dust mites, animal allergens, and pollens, can cause exacerbation, and therefore exposure to them should be minimized. (A)

There is a lower threshold for irritation of the skin in patients with AD.[121] Therefore it is important to identify and avoid irritants that trigger the itch-scratch cycle (Table E2). These include soaps, detergents, chemicals, abrasive clothing, and extremes of temperature and humidity. Alcohol and astringents found in toiletries are drying. Therefore the use of soaps, solvents, and similar compounds should be avoided. When soaps are used, they should have minimal defatting activity and a neutral pH. Mild soaps include unscented Dove, Basis, Neutrogena, Aveeno, Purpose, CeraVe, Eucerin, Vanicream, and Cetaphil. New clothing should be laundered before wearing to decrease levels of formaldehyde and other chemicals added for fabric sizing. Residual laundry detergent in clothing might be irritating. Using a liquid rather than powder detergent and adding a second rinse cycle will facilitate removal of the detergent. Occlusive tight clothing should be avoided, and the patient should be advised to wear open-weave, loose-fitting cotton or cotton-blend garments.

Recommendations regarding environmental living conditions should include temperature and humidity control to avoid increased pruritus related to heat, humidity, and perspiration. One goal of treatment is for children to be as normally active as possible. Certain sports, such as swimming, might be better tolerated than sports involving intense perspiration, physical contact, or heavy clothing and equipment, but patients must rinse off the chlorine after swimming immediately and lubricate their skin. Although UV light might be beneficial for some patients with AD, sunscreens should be used to avoid sunburn. However, because sunscreens can be irritants, care should be used to identify a nonirritating sunscreen, such as Vanicream, Neutrogena Sensitive Skin, Aveeno Mineral Block, Blue Lizard Baby, and Badger Unscented Sunscreen. Prolonged sun exposure can lead to evaporative losses or sweating, both of which can be irritating, and can produce photodamage.

Foods and aeroallergens, such as dust mites, animal allergens, and pollens, might trigger AD. The clinician should only test for relevant allergens because testing, especially for foods, has low specificity. Food allergens trigger AD more commonly in young infants and children than in adults. In children less than 5 years old with moderate-to-severe AD, evaluation of food allergy to milk, egg, peanut, wheat, and soy could be considered if the child has persistent AD in spite of optimized management and topical therapy, has a reliable history of an immediate reaction after ingestion of a specific food, or both.[122] Potential allergens can be identified by taking a careful history and performing appropriate immediate hypersensitivity skin tests.[122,123] Intracutaneous skin tests to foods are not recommended because they are relatively nonspecific, can trigger anaphylactic reactions, and do not provide reliable results in this patient population. Negative skin test or *in vitro* test results have a high predictive value for ruling out suspected allergens. On the other hand, positive skin test results, specific IgE test results, or both, particularly to foods, do not always correlate well with clinical symptoms and need to be confirmed with a controlled food challenge.[5,8,124] Extensive elimination diets based only on positive test results should not be recommended because potential nutritional deficiency can occur, and even with multiple positive skin or specific IgE test results, most patients will react to 3 or fewer foods on blinded challenge.[8,125] A recent systematic review of dietary exclusions for AD found 1 prospective controlled study that supported egg elimination in patients with symptoms of egg allergy.[126]

A recent study suggested that the larger the mean wheal size of the skin test, the more likely the food allergen will be of clinical relevance.[127] Studies also indicate that food-specific serum IgE concentrations might be useful for diagnosing symptomatic allergy to certain foods, such as egg, milk, and peanut, and could eliminate the need to perform controlled food challenges in some patients.[128-130] However, the amount of food causing a reaction and the severity of the reaction are not predicted by skin prick testing or concentration of food-specific serum IgE.[131,132] If the

patient has a history suggestive of food allergy but there is no evidence of food-specific IgE antibodies, it might be necessary to perform an oral food challenge to rule out food sensitivity that is not IgE mediated.[133] Specific IgG or IgG_4 antibody testing for the diagnosis of food hypersensitivity does not correlate with food challenges and should not be performed.[122,123]

Pruritus and eczematoid skin lesions can develop after intranasal or bronchial inhalation challenge with aeroallergens in sensitized patients with AD who have specific IgE antibodies against the challenge allergen.[134] Epicutaneous application of aeroallergens (eg, house dust mites, weeds, animal danders, and molds) by means of patch testing on uninvolved skin of patients with AD elicits eczematoid reactions in up to 40% of patients with AD, although the clinical significance of this finding is unclear.[135,136] In contrast, patch test results are usually negative in patients with respiratory allergy and healthy volunteers. Two studies have found that effective reduction in the level of house dust mites is associated with improvement in AD, although some randomized controlled studies have not shown improvement.[137-140] Avoidance of house dust mites might include (1) use of dust mite–proof encasings on pillows, mattresses, and box springs; (2) washing bedding in hot water weekly; (3) removal of bedroom carpeting; and (4) decreasing indoor humidity levels with air conditioning.[141]

Because there are many triggers that contribute to flares of AD, attention should be focused on controlling those trigger factors that are important in each patient; for example, infants and young children are more likely to have food allergy, whereas environmental aeroallergens are more important in causing exacerbation of AD in older children and adults.

MICROBES

Summary Statement 37: The clinician should be aware that skin infections with *Staphylococcus aureus* are a recurrent problem in patients with AD, and patients with moderate-to-severe AD have been found to make IgE antibodies against staphylococcal toxins present in their skin. (B)

Summary Statement 38: The clinician should prescribe a short course of an appropriate systemic antibiotic only for patients who are clinically infected with *S aureus*. In areas with high levels of methicillin-resistant *S aureus*, the clinician might want to obtain a skin culture and initiate treatment with clindamycin, doxycycline, or trimethoprim-sulfamethoxazole while awaiting culture results. (A)

Summary Statement 39: AD can be complicated by recurrent viral skin infections, such as herpes simplex, warts, and molluscum contagiosum. The clinician should diagnose and promptly treat disseminated herpes simplex or eczema herpeticum with systemic antiviral agents. (B)

Summary Statement 40: The clinician should not immunize patients with AD or their household contacts with smallpox vaccination because they can have a severe, widespread, potentially fatal cutaneous infection called eczema vaccinatum, which is similar in appearance to eczema herpeticum. (C)

Summary Statement 41: The clinician should consider fungal infections that can complicate AD and might contribute to exacerbations. The diagnosis of dermatophytes can be made by using KOH preparation or culture. *Malassezia* species, which is a particular problem in young adults with refractory head and neck eczema, can be diagnosed clinically or with a KOH preparation. Specific IgE to *Malassezia* species might also be obtained. (C)

Skin infections, particularly with *S aureus*, can be a recurrent problem in patients with AD, requiring specific treatment. Patients with moderate-to-severe AD have been found to make IgE antibodies against staphylococcal toxins present on their skin.[142-144] Only in patients with extensive infection is a course of systemic antibiotics.[15,145] For patients with *S aureus* infections, a penicillinase-resistant penicillin (dicloxacillin, oxacillin, or cloxacillin) is usually first-line therapy. Cephalosporins also offer effective coverage for both staphylococci and streptococci[146] and are more palatable for young children. In areas with high levels of methicillin-resistant *S aureus*, an appropriate approach is to obtain skin cultures and initiate clindamycin, doxycycline, or trimethoprim-sulfamethoxazole while waiting culture results.[147]

Patients with high *S aureus* colonization might benefit from a combination of anti-inflammatory treatment and local antiseptics, such as triclosan, chlorhexidine, or gentian violet 0.3% or from the use of bleach baths (see Summary Statement 33).[120,148,149] In small studies the use of silver-coated textiles and silk fabric with an antimicrobial finish was shown to reduce *S aureus* colonization and eczema severity as well.[150,151] Increased binding of *S aureus* to skin is probably related to the underlying inflammation present in patients with AD. This is supported by the observation that treatment with topical glucocorticoids or tacrolimus reduces *S aureus* counts on atopic skin.[86,152] Recent studies have demonstrated that T_H2 immune responses increase binding of *S aureus* to inflamed skin lesions and reduce local innate immune responses needed to kill *S aureus*.[153,154]

AD can be complicated by recurrent viral skin infections, such as herpes simplex, warts, and molluscum contagiosum, which might reflect local defects in T-cell function.[39,155] Herpes simplex, resulting in Kaposi varicelliform eruption or eczema herpeticum, can be a serious infection. The presence of punched-out erosions, vesicles, and/or infected skin lesions that do not respond to oral antibiotics should initiate a search for herpes simplex. Herpes simplex infection can be diagnosed by a Giemsa-stained Tzanck smear of cells scraped from the vesicle base, commercial immunofluorescence assays, or viral culture. Antiviral treatment for cutaneous herpes simplex infections with acyclovir administered intravenously or any of the alternative therapeutic options is of critical importance in the patient with widespread AD because life-threatening dissemination has been reported.[155-157] In patients with AD, smallpox vaccination or even exposure to recently vaccinated subjects can cause a severe, widespread, life-threatening dermatitis called eczema vaccinatum, which is similar in appearance to eczema herpeticum.[158,159] In the event of a smallpox bioterrorist attack, patients with AD would be at increased risk for this complication.

Dermatophyte infections can complicate AD and might contribute to exacerbation of the disease. They could be diagnosed by using a KOH preparation or by fungal culture. There has been particular interest in the role of *Malassezia sympodialis (Pityrosporum ovale)* in patients with AD. *M sympodialis* is a lipophilic yeast commonly present in the seborrheic areas of the skin and scalp. IgE antibodies against *M sympodialis* are commonly found in patients with AD, most frequently in patients with involvement of the head and neck area.[160,161] *Malassezia* species is difficult to culture but can be seen on a KOH preparation. Cross-reactivity between the stress-inducible enzyme manganese superoxide dismutase of human and fungal origin might lead to autoreactivity

and further aggravate the course of AD.[162] Systemic treatment with ketoconazole in patients with AD and a positive skin prick test response or with specific IgE against *M sympodialis* leads to a reduction of the SCORAD score.[163] Treatment of head-neck-shoulder dermatitis with topical ciclopirox olamine had a positive effect in another study.[164]

QUALITY OF LIFE AND EMOTIONAL STRESS

Summary Statement 42: The clinician should recognize that AD has a significant effect on patient and family quality of life and that patients have an increased risk for psychological distress. The clinician should ask about stress and emotional factors, which can cause exacerbations and have been found to induce immune activation, as well as to trigger pruritus and scratching. (C)

Summary Statement 43: The clinician should assess for sleep disturbances. Sleep might improve with treatment of inflammation, but the clinician might also consider therapeutic agents or referral to a sleep specialist or psychologist in severe cases or when sleep does not improve in remission. (C)

AD has a significant effect on patient and family quality of life, with commonly reported stressors, including pruritus and scratching, avoidance of daily activities, embarrassment about appearance, and financial costs, time demands, and lifestyle changes, associated with management.[165-169] Patients might be at increased risk for emotional distress and behavioral problems, such as fussiness, irritability, and clinginess in young children,[165,170] as well as anxious and depressive symptoms.[171-173]

Sleep disruption caused by pruritis and scratching is common and includes difficulty falling asleep, frequent awakenings, overall reduced sleep efficiency, difficulty waking in the morning, and daytime tiredness.[174,175] Sleep disturbances have been associated with increased daytime behavior problems and might mediate an increased risk for ADHD in children with AD.[175,176] Awakenings may persist even in remission, suggesting the role of learned sleep patterns in maintaining sleep disturbances for some patients.[177] Sleep often improves with effective anti-inflammatory treatment of AD.[178,179] Use of wet-wrap therapy at bedtime might be helpful in reducing pruritis and serving as a protective barrier against scratching.[84] Sedating antihistamines might offer an advantage for some patients when used at bedtime, and other therapeutic agents might be useful on a short-term basis.[180] In the case of patients for whom sleep does not improve along with the condition of the skin, the clinician should consider referral for a sleep evaluation, behavioral modification, or both.

Although stress and emotional factors do not cause AD,[181,182] they can cause exacerbations and have been found to induce immune activation in patients with this condition.[183-185] Patients often respond to stress with increased pruritus and scratching. In some patients scratching occurs out of habit. Psychological evaluation, therapy, or both should be considered in patients who have difficulty with emotional triggers of scratching or skin flares or for whom psychological distress negatively affects treatment adherence. Although there have been only a limited number of robustly designed trials of psychological interventions as adjuncts to conventional therapy for AD, there is some evidence to suggest that relaxation, habit reversal (identifying situations that provoke scratching and substituting competing responses), stress management, or biofeedback might be helpful in reducing disease severity, pruritus, and scratching, particularly for patients with a high level of pretreatment scratching.[186,187] Parents might benefit from psychoeducation regarding strategies to minimize children's scratching behavior and increase patient cooperation with skin care.[188,189]

PATIENT EDUCATION

Summary Statement 44: To achieve effective control of AD, the clinician should educate patients and family members about the chronic nature of the disease, exacerbating factors, and the safety/side effects of the medications. The clinician should also provide demonstrations of skin-care techniques, written treatment plans, and information about patient support organizations. (D)

To achieve effective control of AD, it is important to educate patients and family members about the chronic nature of the disease, exacerbating factors, and appropriate treatment options, including discussion of side effects of and potency of topical corticosteroids. Demonstration of skin-care techniques and observation of the patient's or parents' technique might reduce errors that negatively affect the response to treatment.[84] There is evidence for the effectiveness of educational strategies in improving disease severity and treatment adherence in studies of nurse-led educational sessions and multidisciplinary parent education programs.[62,190-193] Written information that includes detailed skin-care recommendations and methods for environmental control can be helpful.[194] Written plans should include guidelines on how to monitor AD, how to respond to changes in disease status, and when to seek additional medical help. The treatment plan should be reviewed during each follow-up visit, and the patient or parent should demonstrate an appropriate level of understanding to ensure a good outcome. Adequate time and teaching materials are necessary to provide effective education. Patient support organizations that provide educational information and updates on progress in AD research are important resources for these patients. Educational pamphlets and videos can be obtained from the National Eczema Association (4460 Redwood Highway, Suite 16D, San Rafael, CA 94903-1953; 800-818-7546; www.nationaleczema.org), a national, nonprofit, patient-oriented organization, or from the American Academy of Dermatology's Web site EczemaNet (www.skincarephysicians.com/eczemanet).

TREATMENT OF THE DIFFICULT-TO-MANAGE PATIENT

Consultation

Summary Statement 45: The clinician should refer patients refractory to first-line therapy to an AD specialist. (D)

Cooperation between the patient and/or the patient's caregiver or caregivers, primary care physician, and the allergist, dermatologist, or both is important in the implementation of strategies necessary for the care of patients with chronic AD. Consultation with an allergist, dermatologist, or both is recommended (1) for patients with severe AD who have significant dysfunction as a result of their skin disease; (2) for identification or ruling out allergic triggers; (3) for in-depth patient education; (4) when the diagnosis of AD is in doubt; and (5) for implementation of alternative therapies.

Wet dressings

Summary Statement 46: The clinician should recommend application of wet-wrap dressings in combination with topical corticosteroids for treatment of refractory AD. (A) Wet

dressings help with skin barrier recovery, increase the efficacy of topical steroids when used concomitantly, and protect the skin from persistent scratching, allowing more rapid healing of excoriated lesions. (B)

Wet dressings can be used on severely affected or chronic lesions refractory to skin care.[18,20] Dressings can serve as an effective barrier against persistent scratching and promote healing of inflamed or excoriated lesions. Application of wet-wrap dressings in combination with topical corticosteroids has been found to be efficacious in the treatment of refractory AD because of better local activity.[195] Wet-dressing therapy should not be overused because it can result in skin maceration, folliculitis, and secondary infections or rarely adrenal suppression when wet wraps are used for prolonged periods in combination with potent corticosteroids. Wet-dressing therapy is currently not recommended with topical calcineurin inhibitors. A detailed description of wet-wrap therapy is discussed in Boguniewicz et al.[84]

Systemic immunomodulating agents

Summary Statement 47: Immunomodulating agents, such as cyclosporine, mycophenolate mofetil, azathioprine, IFN-γ, and corticosteroids, have been shown to provide benefit for patients with severe refractory AD, although the clinician should consider their potential serious adverse effects. (A)

Cyclosporin A. Systemic cyclosporin A is a potent immunosuppressive drug that acts primarily on T cells by suppressing cytokine gene transcription. The drug binds to an intracellular protein, cyclophilin, and this complex in turn inhibits calcineurin, a molecule required for initiation of cytokine gene transcription. Several randomized controlled studies have demonstrated that both children and adults with severe AD refractory to conventional treatment can benefit from short-term treatment with oral cyclosporin A (5 mg/kg per day) in terms of reduced skin disease and improved quality of life.[196-198] However, adverse effects (nausea, abdominal discomfort, hypertrichosis, paresthesias, hypertension, hyperbilirubinemia, and renal impairment) dictate caution in the use of this drug. Furthermore, discontinuation of treatment can result in relapse of skin disease.[199] A meta-analysis of 15 studies including 602 patients found that cyclosporin A consistently decreased the severity of AD in all studies analyzed.[23] After 2 weeks of treatment, the authors found a dose-related response with a pooled mean decrease in disease severity of 22% (95% CI, 8% to 36%) with low-dose cyclosporin A (≤3 mg/kg) and 40% (95% CI, 29% to 51%) at dosages of 4 mg/kg or greater. After 6 to 8, weeks the relative effectiveness was 55% (95% CI, 48% to 62%).

Mycophenolate mofetil. Mycophenolate mofetil is a purine biosynthesis inhibitor with immunosuppressive activity that has been used for the treatment of refractory inflammatory skin disorders.[200,201] Short-term oral mycophenolate mofetil (2 g/d) as monotherapy has been reported in open-label studies to clear skin lesions in some adults with AD resistant to other treatment, including topical and oral steroids and PUVA. The drug has generally been well tolerated, with the exception of occasional herpes retinitis and dose-related bone marrow suppression. An observer-blinded, randomized controlled trial compared enteric coated mycophenolate sodium with cyclosporin A as long-term treatment in adult patients with severe AD.[24] Fifty-five patients with AD were treated with cyclosporin A (5 mg/kg) in a 6-week run-in period and then patients received either cyclosporin A (3 mg/kg, n = 26) or enteric coated mycophenolate sodium (1440 mg, n = 24) during a 30-week maintenance phase with a 12-week follow-up period. During the first 10 weeks, the objective SCORAD scores and serum thymus and activation-regulated chemokine levels in the enteric coated mycophenolate sodium study arm were higher in comparison with those seen in the cyclosporin A study arm. In addition, 7 of the 24 patients treated with enteric coated mycophenolate sodium required short corticosteroid courses. During the maintenance phase, disease activity was comparable in both study arms. Side effects in both study arms were mild and transient. After study medication withdrawal, disease activity of the patients in the cyclosporin A study arm significantly increased compared with that seen in the enteric coated mycophenolate sodium study arm. A retrospective analysis of 14 children with AD treated with mycophenolate mofetil as systemic monotherapy found that 4 (29%) patients achieved complete clearance, 4 (29%) patients had greater than 90% improvement (almost clear), 5 (35%) patients had 60% to 90% improvement, and 1 (7%) patient did not respond.[202] Initial responses occurred within 8 weeks (mean, 4 weeks), with maximal effects attained after 8 to 12 weeks (mean, 9 weeks) at mycophenolate mofetil doses of 40 to 50 mg/kg/d in younger children and 30 to 40 mg/kg/d in adolescents. Mycophenolate mofetil was well tolerated in all patients, with no infectious complications or laboratory abnormalities.

Azathioprine. Azathioprine is a purine analog with anti-inflammatory and antiproliferative effects that has been used for the treatment of severe AD.[25,203] A double-blind, placebo-controlled crossover study in adult patients with severe AD showed a 27% mean reduction in disease activity after 12 weeks of treatment with 2.5 mg/kg azathioprine.[204] Myelosuppression is a significant adverse effect, and thiopurine methyltransferase levels might predict subjects at risk for this adverse effect.[25,205,206] A systematic review of 10 studies of azathioprine in 319 patients with moderate-to-severe refractory AD showed an overall decrease in disease severity after active treatment with azathioprine.[207] Two of the included randomized controlled trials showed that azathioprine was significantly better than placebo. A recent randomized, assessor-blinded trial in patients with severe AD found azathioprine (1.5-2.5 mg/kg/d) to be comparable in clinical efficacy to methotrexate (10-22.5 mg/wk) after 12 weeks of treatment.[208]

IFN-γ. IFN-γ is available as a recombinant molecule for the treatment of chronic granulomatous disease. It is also known to downregulate T_H2 cell function. Studies of patients with AD have demonstrated that treatment with recombinant IFN-γ results in clinical improvement and decreases total circulating eosinophil counts.[209,210] In one study a small subset of patients showed persistent improvement 3 months after treatment was discontinued.[211] Reduction in the clinical severity of AD correlated with the ability of IFN-γ to decrease blood eosinophilia. In another study in which patients with AD were treated for up to 24 months, total body surface involvement decreased from 62% at baseline to 18.5% after 24 months of treatment.[212] Long-term therapy was not associated with any significant laboratory abnormalities or clinical adverse events. However, influenza-like symptoms are commonly observed adverse effects early in the treatment course and limit the use of this therapy.

Systemic corticosteroids. The use of systemic corticosteroids, such as oral prednisone, might be required in the treatment of severe chronic AD, although there is a paucity of controlled studies, despite widespread use of this therapy. In a double-blind, placebo-controlled, crossover trial of 26 children with severe AD, those receiving 4 weeks' treatment with combined oral plus nasal

beclomethasone dipropionate improved significantly more than those receiving placebo.[213] No adverse effects were observed, but 24-hour urinary cortisol excretion was slightly reduced. In another pediatric study 20 children with chronic severe AD were treated with systemic flunisolide in a multicenter, randomized, double-blind, placebo-controlled, crossover study.[214] Patients' clinical severity scores improved significantly after 2 weeks of flunisolide treatment compared with placebo. After treatment with flunisolide, no worsening of symptoms or relapse occurred. No side effects were observed during the study. In a different approach to systemic corticosteroid therapy in pediatric patients, intravenous bolus therapy with 20 mg/kg/d methylprednisolone for 3 days resulted in improvement in 5 of 7 patients without significant side effects.[215] Nevertheless, the PRACTALL consensus report states that in cases of acute flare-up, while patients might benefit from a short course of systemic therapy with corticosteroids, long-term use and use in children should be avoided.[216] A recent comparison study of oral prednisolone versus cyclosporine in adults found a high rebound exacerbation rate in patients treated with prednisolone in spite of the use of moderate-potency topical steroids and emollients.[217] Clinical improvement with systemic corticosteroids is often associated with rebound flaring of AD after discontinuation. If a short course of oral corticosteroid therapy is given for a patient with severe AD, it is important to taper the dosage as it is discontinued. Intensified skin care with topical anti-inflammatory therapy should also be instituted during the corticosteroid taper to suppress rebound flaring of AD.

Methotrexate. Methotrexate is a folic acid antagonist that interferes with purine and pyrimidine synthesis, which is essential for DNA and RNA synthesis. Methotrexate has been shown to be effective in patients with moderate-to-severe AD. In an open-label, dose-ranging study involving 12 patients, a decrease in disease activity by 52% from baseline was observed after 24 weeks.[218] The median dose was 15 mg/wk. Eight patients experienced a persistent improvement of greater than 12 weeks after stopping therapy. In a retrospective study 75% of patients treated intramuscularly with weekly doses of 7.5 to 25 mg of methotrexate had clinical improvement of greater than 70%, as assessed by a physician after 3 months of therapy.[219] In another retrospective study of low-dose methotrexate therapy with 10 to 25 mg/wk for 8 to 12 weeks, 80% of patients with moderate-to-severe AD had a mean decrease in SCORAD scores of 44%.[220] A recent randomized, assessor-blinded trial in patients with severe AD found methotrexate (10-22.5 mg/wk) to be comparable in clinical efficacy to azathioprine (1.5-2.5 mg/kg/d) after 12 weeks of treatment.[208] Symptom improvement in responders can be seen as early as 2 weeks and up to 3 months after initiating therapy. The studies suggest that patients not responding to 15 mg of methotrexate per week after 3 months are unlikely to improve with further dose escalation.[218] Nausea and liver enzyme increases are the most common adverse events that result in transient or complete discontinuation of methotrexate therapy.

Phototherapy

Summary Statement 48: UV therapy can be a useful treatment for recalcitrant AD. The most effective phototherapy option that is available in the United States is narrow-band UVB. (A) The clinician should consider referral to a center with phototherapy availability.

UV light therapy can be a useful treatment of chronic and recalcitrant AD but should be done under the supervision of a dermatologist experienced in such treatment. The most commonly used phototherapy modalities are narrow-band UVB, broadband UVB, and UVA1.[21,221,222] Short-term adverse effects from phototherapy can include erythema, skin pain, pruritus, and pigmentation. Potential long-term adverse effects include premature skin aging and cutaneous malignancies.

In an open trial in patients with moderate-to-severe chronic AD, all patients had a 50% or greater reduction in SCORAD scores with narrow-band UVB phototherapy administered 3 times weekly for up to 12 weeks.[22] Lesional and nonlesional skin biopsy specimens were obtained before and after treatment. Gene expression and immunohistochemistry studies showed that T_H2, T22, and T_H1 immune pathways were suppressed and that measures of epidermal hyperplasia and differentiation normalized. The reversal of disease activity was associated with elimination of inflammatory leukocytes and T_H2/T22- associated cytokines and chemokines and normalized expression of barrier proteins. A retrospective review of children with severe eczema who had undergone narrow-band UVB found that of those who completed more than 10 exposures, complete clearance or minimal residual activity was achieved in 40%, good improvement was achieved in 23%, and moderate improvement was achieved in 26%.[223] Overall, the treatment was well tolerated, and the median length of remission was 3 months. A prospective analysis of narrow-band UVB phototherapy found that it was an effective and well-tolerated treatment modality in children.[224]

UVA1 phototherapy has been shown to be effective for acute exacerbations of AD.[225] A systematic review of phototherapy in patients with AD found that UVA1 should be used to control acute flares of AD, whereas UVB modalities, specifically narrow-band UVB, should be used for the management of chronic AD.[226] A 6-week course of medium-dose UVA1 and narrow-band UVB in a randomized, double-blind, controlled crossover trial showed no significant difference between treatments with respect to clinical scores, pruritus scores, or health-related quality of life.[227] In a randomized, investigator-blinded, half-sided comparison study between narrow-band UVB and medium-dose UVA1 in adults with AD, both modalities significantly decreased clinical severity ($P < .01$) and dermal cellular infiltrates.[228]

Photochemotherapy with PUVA should be restricted to patients with severe widespread AD, although studies comparing it with other modes of phototherapy are limited. In one randomized, observer-blinded crossover trial, PUVA was shown to provide better short- and long-term responses than medium-dose UVA1 in patients with severe AD.[229] Patients received either 15 exposures to medium-dose UVA1 as the first treatment and, in cases of relapse, another 15 exposures to PUVA as the second treatment or *vice versa*. All patients were followed until 12 months after discontinuation of the last treatment. Although both phototherapies resulted in clinical improvement, PUVA reduced the baseline SCORAD score to a significantly greater extent than UVA1 ($P = .041$). The median length of remission was 4 weeks after UVA1 and 12 weeks after PUVA therapy ($P = .012$).

Hospitalization

Summary Statement 49: The clinician might consider hospitalization, which can result in an improvement in AD by removing the patient from environmental allergens, irritants, and stressors and by providing patient/caregiver education,

addressing sleep disturbance and psychosocial issues, intensifying treatment, and improving adherence with the treatment regimen. (D)

Patients with moderately severe nonresponsive AD who appear erythrodermic or have widespread severe skin disease resistant to outpatient therapy might require hospitalization. In many cases removing the patient from environmental allergens or irritants, intense patient education, and assurance of compliance with therapy result in sustained improvement. Clearing of the patient's skin during hospitalization also allows the patient to undergo allergen skin testing and appropriately controlled provocative challenges to correctly identify potential allergens.

Allergen immunotherapy

Summary Statement 50: On the basis of several studies of dust mite immunotherapy, the clinician might consider allergen immunotherapy in selected patients with AD with aeroallergen sensitivity. (B)

Summary Statement 8 from the immunotherapy practice parameter states that there are some data indicating that immunotherapy can be effective for AD when this condition is associated with aeroallergen sensitivity.[230]

Several studies suggest that immunotherapy could be effective for the treatment of AD associated with aeroallergen sensitivity.[231] In a systematic review of immunotherapy for AD that included 4 comparable placebo-controlled studies involving a small number of patients, statistical analysis showed significant improvement in symptoms in patients with AD who received subcutaneous immunotherapy.[231,232] One randomized, double-blind study of adults with AD demonstrated a dose-response effect of dust mite immunotherapy on AD severity, as measured by using the SCORAD score ($P = .0378$) and topical corticosteroid use ($P = .0007$).[233] One open-label study of 25 patients with dust mite allergy and AD treated with dust mite subcutaneous immunotherapy demonstrated serologic and immunologic changes consistent with tolerance in addition to significant reductions in objective and subjective SCORAD scores.[234] In addition, 1 double-blind, placebo-controlled study of 48 children with AD treated with dust mite sublingual immunotherapy reported a significant difference from baseline values in visual analogue scores, SCORAD scores, and medication use in the mild-to-moderate severity group, whereas patients with severe disease had only a marginal benefit.[235]

Investigative approaches

Summary Statement 51: There are investigative treatments (intravenous immunoglobulin, omalizumab, and rituximab) that have been proposed for the management of AD. We do not recommend using them because they remain unproved at this time.

Intravenous immunoglobulin. High-dose intravenous immunoglobulin has been shown to have immunomodulatory activity in patients with AD, and in addition, intravenous immunoglobulin can interact directly with microbes or toxins involved in the pathogenesis of this disease. Intravenous immunoglobulin has been shown to contain high concentrations of staphylococcal toxin–specific antibodies that inhibit the *in vitro* activation of T cells by staphylococcal toxins.[236] Treatment of severe refractory AD with intravenous immunoglobulin has yielded conflicting results. Most studies have not been controlled and have involved small numbers of patients.[237] Although children appear to have a better response than adults, controlled studies are needed to answer the question of efficacy in a more definitive manner. In a randomized, placebo-controlled study 48 children with moderate-to-severe AD were treated with 3 injections of 2 g/kg intravenous immunoglobulin or placebo at 1-month intervals over a 12-week period.[238] Assessments were conducted after each injection and at 3 and 6 months after completion of treatment. The disease severity index was significantly decreased 3 months after completing treatments compared with baseline values ($P < .05$). However, improvement decreased by 6 months after therapy.

Omalizumab. Case reports and small case series in patients with AD have shown both clinical benefit and lack of improvement.[224,239-244] The study by Belloni et al[239] could not identify any specific markers to identify responders to omalizumab therapy. A prospective analysis assessed the efficacy of omalizumab in 21 patients 14 to 64 years of age with moderate-to-severe persistent allergic asthma and AD.[245] AD severity was assessed at 0, 1, 3, 6, and 9 months by means of investigator global assessment. Pretreatment serum IgE levels ranged from 18.2 to 8396 IU/mL, with a mean level of 1521 IU/mL. All 21 patients showed clinical and statistically significant improvement of their AD ($P < .00052$). However, a placebo-controlled trial of omalizumab in 20 patients with AD for 16 weeks did not show significant clinical benefit.[246]

Rituximab. Rituximab, a chimeric anti-CD20 mAb originally developed for the therapy of B-cell malignancies, has been used in patients with AD in an open trial.[247] Six patients with severe AD received 2 intravenous infusions of 1000 mg of rituximab administered 2 weeks apart. All patients showed an improvement of their skin symptoms within 4 to 8 weeks, and their eczema area and severity index decreased significantly ($P < .001$). Histology of skin biopsy specimens showed significant improvement in spongiosis and acanthosis, and dermal T- and B-cell infiltrates decreased as well. Of note, whereas circulating B cells were at less than detectable levels as a consequence of rituximab therapy, lesional B-cell counts were reduced by approximately 50%. Expression of IL-5 and IL-13 was also reduced after therapy. Although total serum IgE levels were reduced, allergen-specific IgE levels were not affected. The safety and long-term efficacy of a single dose of 1000 mg of rituximab was also reported in a pregnant women treated in her first trimester before a positive pregnancy test.[248] In contrast, treatment with 500 mg of rituximab administered intravenously twice over a 2-week interval to 2 patients with severe AD resulted in only a transient improvement in clinical scores, followed by deterioration.[249]

ANNOTATIONS TO FIG 1

Annotation 1: Patient presents with skin manifestations consistent with AD (eg, an eczematous pruritic dermatitis)

There is no objective laboratory test for the diagnosis of AD. Therefore the diagnosis of AD is based on a constellation of clinical features. These include (1) the essential feature, which is pruritic dermatitis, and (2) typical features, such as facial and extensor eczema in infants and children or flexural eczema at any age and (3) chronic or relapsing dermatitis. Other frequently associated features include a personal or family history of atopic disease, xerosis, cutaneous infections, increased serum IgE levels, positive immediate-type allergy skin test results, and early age of onset.

Annotation 2: Evaluation based on history and physical examination diagnostic for AD

AD often is associated with an early age of onset, with approximately 80% of cases starting before the age of 5 years. Frequently, it is associated with respiratory allergy and a number of other features, such as Dennie-Morgan infraorbital folds, white dermatographism, hyperlinear palms, and facial pallor.

Acute and subacute lesions of AD are characterized by intensely pruritic, erythematous papulovesicles associated with excoriation and serous exudate. Lesions that do not appear papulovesicular clinically typically demonstrate spongiosis histologically. Chronic AD is characterized by lichenification, papules, plaques, and excoriations. At all stages of AD, patients usually have dry xerotic skin.

Annotation 3: Consideration of other conditions

A firm diagnosis of AD depends on the exclusion of other skin conditions with similar symptoms and signs. Failure of any response to "standardized" management of AD is a reason to consider other eczematous conditions. Skin conditions that can mimic AD fall into the following categories: (1) chronic dermatoses, such as seborrheic dermatitis, irritant or allergic contact dermatitis, nummular eczema, psoriasis, and ichthyoses; (2) infections and infestations, such as scabies, HIV, and dermatophytosis; (3) malignancies, such as cutaneous T-cell lymphoma; (4) immunologic disorders, such as dermatitis herpetiformis, graft-versus-host disease, and dermatomyositis; (5) immunodeficiencies, such as Wiskott-Aldrich syndrome, severe combined immunodeficiency disease, hyper-IgE syndrome, Netherton syndrome, and DiGeorge syndrome; and (6) metabolic disorders, such as zinc, pyridoxine, or niacin deficiency and phenylketonuria. In situations in which the diagnosis is not obvious, a skin biopsy should be considered. The skin biopsy should be performed by a physician trained and experienced in performing the procedure and should be interpreted by a qualified dermatopathologist.

Annotation 4: Is the AD severe?

Severe AD is characterized by intensely pruritic widespread skin lesions that often are complicated by persistent bacterial, viral, or fungal infections. The presence of keratoconus, keratoconjunctivitis, anterior cataracts, and eczema herpeticum or eczema vaccinatum suggests that the AD is particularly severe and chronic.

The extent and severity of AD can be determined by careful examination of the patient's skin, grading the extent of the affected areas (eg, percentage of involvement of the head, upper limbs, trunk, and lower limbs) and defining the severity of the following signs of eczema: induration, erythema, excoriation and lichenification, scaling, oozing, and crusting. In general, patients who have more than 20% skin involvement (or 10% skin involvement if affected areas include the eyelids, hands, or intertriginous areas) that has not been responsive to first-line treatment should be considered for consultation with a specialist. Other patients who should be considered as having severe AD include:

- patients with extensive skin involvement who are at risk for exfoliation;
- patients who require ongoing or frequent treatment with high-potency topical glucocorticoids;
- patients who require hospitalization for severe eczema or skin infections related to AD;
- patients with ocular or infectious complications;
- patients who have significant disruption of their quality of life (eg, sleepless nights or school or work days lost); and
- patients who are generally erythrodermic.

Patients not previously receiving appropriate treatment for AD should be started on first-line therapy, and attempts should be made to identify potential triggers.

Annotation 5: Management of AD

The treatment of AD is directed at symptom relief and reduction of cutaneous inflammation. Characterization of each patient's skin disease severity and reduction of exacerbating factors are critical for effective management. All patients require skin hydration in combination with an effective moisturizer. Potential trigger factors should be identified and eliminated. These include irritants, allergens, and emotional stressors. Therapy must be individualized and is dependent on whether the patient is experiencing an acute flare or dealing with the management of chronic AD. The severity of AD is based on the extent of skin involvement, the intensity of pruritus, the presence of complications, the effect on quality of life, and the amount of medication required for control.

The initial management of AD can consist of the following categories of treatment: hydration, topical corticosteroids, tar preparations, antihistamines, topical calcineurin inhibitors, and dilute bleach baths. There are many factors that can contribute to exacerbations of AD, including food allergens, aeroallergens, infections, temperature, humidity, irritants, and emotional stress.

Skin testing or *in vitro* testing for IgE antibodies can be useful in the identification of potential allergens. In particular, negative skin test or *in vitro* test results can be used to exclude allergic trigger factors. Positive skin test or *in vitro* test results do not prove that a particular allergen causes clinical symptoms, but they might guide the clinician in considering possible triggers. This is particularly true in the case of foods, where controlled food challenges might be needed to confirm or exclude clinical sensitivity to foods.

Skin infections should be treated with short courses of appropriate antimicrobial therapy, with an emphasis on appropriate treatment for staphylococcal infections. Cutaneous infections with a number of viruses (herpes simplex and molluscum contagiosum) and fungi (yeast and dermatophytes) also need to be considered and treated after the appropriate diagnosis has been confirmed.

Annotation 6: Is the management successful?

Response to therapy can be classified as a complete response, a partial response, or a treatment failure. Complete response and eradication of the patient's eczema in the short term is unusual unless there is a clear-cut trigger. AD is a chronic relapsing skin condition, and therefore most patients will have a partial response with reduction in pruritus and the extent of skin disease. These patients will need long-term follow-up for adjustment of medications according to the severity of the illness. Patients who do not respond to treatment should be completely reassessed to be certain of the diagnosis, and alternative treatment should be considered.

Annotation 7: Follow-up

It is important to educate patients and family members about the chronic nature of their disease, exacerbating factors, and appropriate treatment options to achieve effective control of the patient's AD. This is important to ensure cooperation and compliance with the treatment plan. Written information that includes detailed skin-care recommendations, environmental control, and general information about the disease should be provided. Patients should be educated on how to monitor their disease and know how to respond to changes in their status and when to seek additional medical help. The treatment plan should be reviewed during follow- up visits, and the patient, parent, or both should demonstrate an appropriate level of understanding to ensure a good outcome. Adequate time and teaching materials are necessary to provide effective education. Patient support organizations that provide updates on progress in AD research are important resources for these patients. Follow-up of patients with AD also should include evaluation for potential triggers of exacerbations (eg, aeroallergens, infection, and emotional factors) and cooperative management with the patient, parent, or both to prevent such exacerbations.

Annotation 8: Reassess: Is the diagnosis of AD correct?

In patients who do not achieve the goals of AD management, it is important to reassess whether the diagnosis is correct. With the lack of a characteristic skin lesion or a confirmatory laboratory test result, the diagnosis depends on clinical symptoms and the physical examination. Concomitant allergic rhinitis, asthma, or both increase the likelihood that the diagnosis of AD is correct. As discussed in Annotation 1, many skin conditions can masquerade as AD. When reassessing patients, it is helpful to consider the following points. Most patients who present with AD are younger than 5 years but are infrequently younger than 6 weeks. Any infant with an eczematous rash presenting earlier than the first month of life should be carefully evaluated for the presence of congenital immunodeficiency, particularly if the course is complicated by recurrent infections and failure to thrive. AD does not usually affect the diaper area or the nose exclusively. It is important to consider contact dermatitis and skin infections as complicating factors.

Annotation 9: Consultation with an AD specialist for consideration of other conditions

Patients who are refractory to first-line therapy and who have severe AD with significant dysfunction should have a consultation with an AD specialist, such as an allergist or dermatologist. Such consultation is recommended when the diagnosis of AD is in doubt and for identification of potential allergen triggers, patient education, and implementation of alternative therapies, including potent anti-inflammatory and immunomodulatory agents.

Cooperation between the patient and/or the patient's guardian or guardians, the primary care physician, and the allergist or dermatologist is important in the implementation of strategies necessary for the care of patients with chronic AD. Even when an AD specialist is consulted, the primary care physician continues to play an important role in the care of patients with AD by ensuring continuity of care.

Annotation 10: Consultation with an AD specialist: Intensification of management and treatment

When AD is either severe or has not responded to appropriate first-line management strategies, specialist consultation should be obtained. This allows both a re-evaluation of adherence to first-line treatment approaches (eg, hydration, moisturizers, and topical corticosteroids) and consideration of alternative therapy. Examples of alternative strategies include (1) the application of wet dressings in combination with topical corticosteroids, (2) phototherapy with ultraviolet light (UVB or UVA [PUVA]), (3) immunomodulatory or immunosuppressive agents, (4) hospitalization to separate the patient from environmental allergens while administering other therapies, and (5) allergen immunotherapy when aeroallergens are clearly implicated in dermatitis flares. In light of potential adverse effects, a careful risk-benefit analysis should be undertaken before initiating any of these alternative therapies. For patients who do not respond to these approaches, investigational treatment can be considered.

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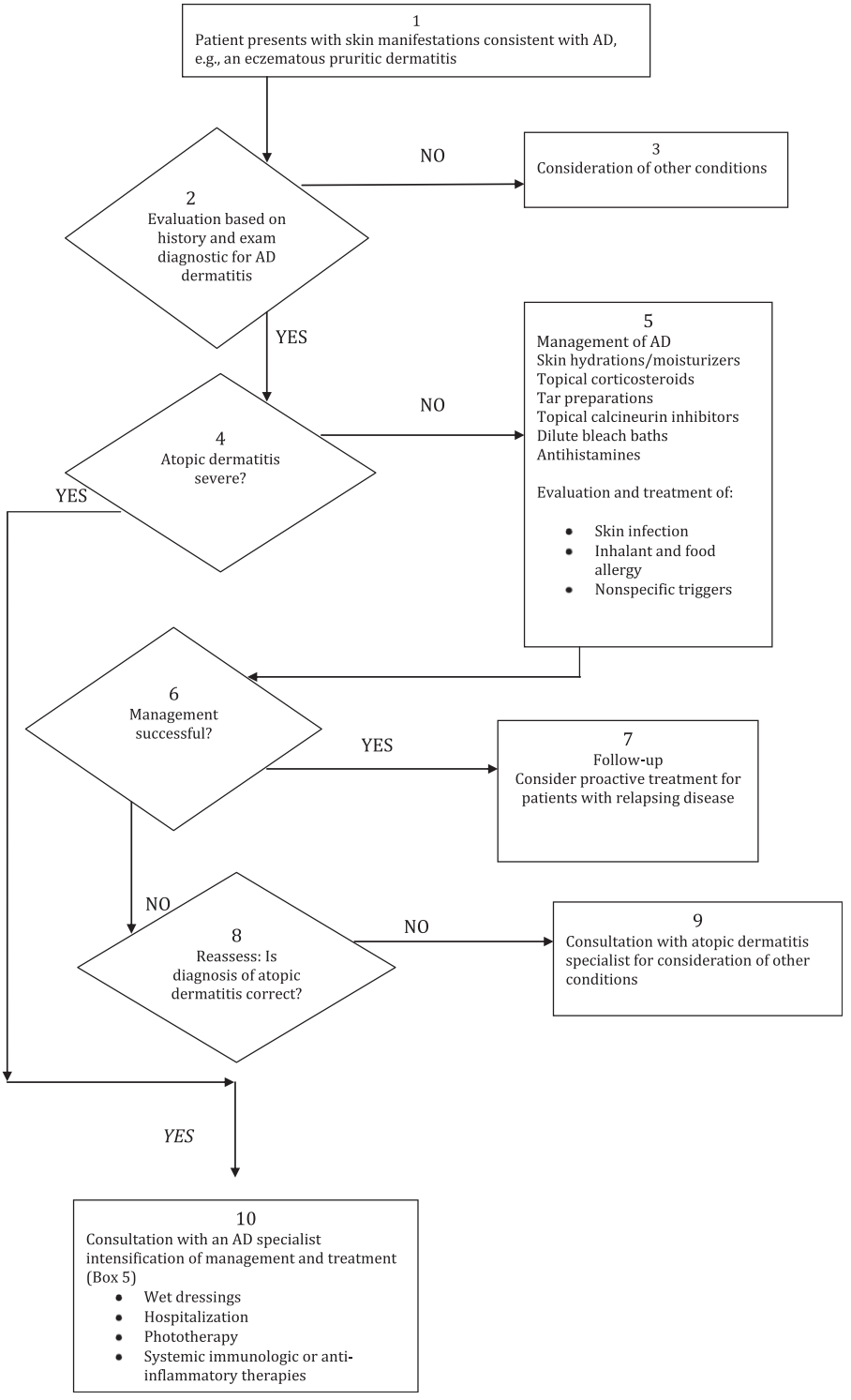

FIG E1. Flow chart of the diagnosis and management of AD.

TABLE E1. Topical glucocorticoid potency ranking

Group I
Betamethasone dipropionate 0.05% (cream and ointment)
Clobestasol propionate 0.05% (cream and ointment)
Diflorasone diacetate 0.05% (ointment)
Halobetasol propionate 0.05% (cream and ointment)
Group II
Amcinonide 0.1% (ointment)
Betamethasone dipropionate 0.05% (cream and ointment)
Desoximetasone 0.25% (cream, gel, ointment)
Diflorasone diacetate 0.05% (ointment)
Fluocinonide 0.05% (cream, gel, ointment, and solution)
Halcinonide 0.1% (cream)
Mometasone furoate 0.1% (ointment)
Group III
Amcinonide 0.1% (cream and lotion)
Betamethasone dipropionate 0.05% (cream)
Betamethasone valerate 0.1% (ointment)
Desoximetasone 0.05% (cream)
Diflorasone diacetate 0.05% (cream)
Fluocinonide 0.05% (cream)
Fluticasone propionate 0.005% (ointment)
Halcinonide 0.1% (ointment and solution)
Triamcinolone acetonide 0.1% (ointment)
Group IV
Hydrocortisone valerate 0.2% (ointment)
Flurandrenolide 0.05% (ointment)
Fluocinolone acetonide 0.025% (ointment)
Mometasone furoate 0.1% (cream)
Triamcinolone acetonide 0.1% (cream)
Group V
Betamethasone dipropionate 0.05% (lotion)
Betamethasone valerate 0.1% (cream)
Fluticasone acetonide 0.025% (cream)
Fluticasone propionate 0.05% (cream)
Flurandrenolide 0.05% (cream)
Hydrocortisone valerate 0.2% (cream)
Prednicarbate 0.1% (cream)
Group VI
Alclometasone dipropionate 0.05% (cream and ointment)
Betamethasone valerate 0.05% (lotion)
Desonide 0.05% (cream)
Flucinolone acetonide 0.01% (cream, oil and solution)
Triamcinolone acetonide 0.1% (cream)
Group VII
Hydrocortisone hydrochloride 1% (cream and ointment)
Hydrocortisone hydrochloride 2.5% (cream, lotion, and ointment)
Hydrocortisone acetate 1% (cream and ointment)
Hydrocortisone acetate 2.5% (cream, lotion, and ointment)
Pramoxine hydrochloride 1.0% (cream, lotion, and ointment)
Pramoxine hydrochloride 2.5% (cream, lotion, and ointment)

TABLE E2. Triggers of itching in patients with AD*

Irritants
1. Lipid solvents (ie, soaps and detergents)
2. Disinfectants
3. Occupational irritants
4. Household fluids (eg, juices from fresh fruits and meats)
5. Wool
Contact and aeroallergens
1. Dust mites, contact allergens > aeroallergens
2. Furry animals (cat and dog)
3. Pollens (seasonal)
4. Molds
5. Human dander (dandruff)
6. Topical therapies
7. Nickel
Microbial agents
1. Viral infections (upper respiratory tract and skin infections)
2. *Staphylococcus aureus* (either as a superantigen or pathogen)
3. *Pityrosporum ovale* yeast
4. *Candida* species (rarely)
5. Dermatophytes (rarely)
Others
1. Foods (as contact irritants > vasodilators > allergens)
2. Psychological stress
3. Climate
4. Hormones (eg, menstrual cycle)
5. Vaccinations

*Not all patients with AD will be triggered by every stimulus. There are subsets of patients with AD who will experience exacerbations caused by some triggers and not by others. Adapted from Beltrani VS. The clinical spectrum of atopic dermatitis. J Allergy Clin Immunol 1999;104(suppl):S87-S98.