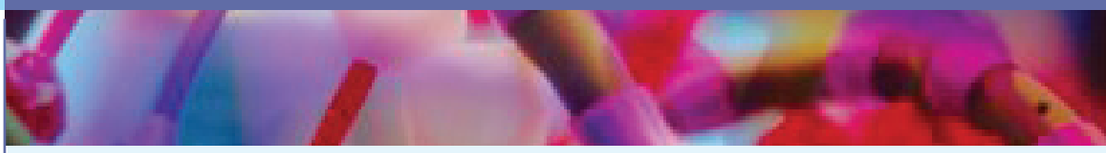
NATIONAL JEWISH Medical and Research Center

Advances in Our Understanding and Management of Atopic Dermatitis



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Learning Objectives:

At the conclusion of this activity, participants should be able to:

- Recognize the prevalence of atopic dermatitis (AD), its impact on quality of life, and its association with asthma and allergies.
- Examine a multi-faceted approach to management of patients with AD including nonpharmacologic and pharmacologic interventions.
- Describe the role of topical calcineurin inhibitors in AD, address safety issues including the boxed warning and optimal use of these agents.

Introduction

Atopic dermatitis (AD), also known as atopic eczema, is the most common chronic, relapsing skin disorder seen in infants and children, although it can affect patients of any age. AD is associated with dry, easily irritated, itchy skin leading to scratching, chronic skin rashes, disruption of sleep and reduction in quality of life. This skin condition often occurs in people who have asthma, hayfever, or food allergies, or in family members of people who have allergic conditions. AD has been steadily increasing in prevalence for the past 3 decades and now affects 15–20% of children in industrialized countries. Several longitudinal studies suggest that AD patients are predisposed to the development of asthma and allergic rhinitis (the so-called "atopic march"). Therefore, effective treatment of AD is being explored as 1 strategy to prevent the atopic march. This review will examine our current understanding of AD and strategies being used at National Jewish Medical and Research Center in Denver, Colorado to manage this common skin disease.

Clinical Features of AD

The onset of AD often occurs during infancy and early childhood. These children frequently have a family history of asthma, hay fever, or food allergy. The cardinal feature of AD is pruritus or itching that disrupts sleep and interferes with daily activities. The rash has 3 distinct clinical phases: infantile, childhood, and adulthood. Each of the phases is characterized by a typical distribution pattern and appearance.

The infantile phase occurs from infancy until 2 to 3 years of age. AD in infants usually starts on the cheeks, scalp, wrists, extensor aspects of the legs, and neck. Involvement of the trunk is common, but the diaper area is typically spared. Infantile AD lesions tend to be symmetric, scaly, and erythematous.

Target Audience:

This activity is intended for primary care physicians and pediatricians

Accredditation

National Jewish Medical and Research Center is accredited by the ACCME to provide continuing medical education for physicians.

National Jewish Medical and Research Center designates this educational activity for a maximum of [number of credits] *AMA PRA Category 1 Credits(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Term of Approval:

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NOVARTIS

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Case Presentation

A 3-year-old male presents with an itchy, red, eczematous rash. Current skin care regimen includes a short bath without any cleanser 2–3 times/week followed by application of lotion. Mometasone 0.1% ointment is applied to areas of eczema on the body as needed 2–3 times daily.

Past Medical History:

- Treated with antibiotics twice for weepy skin lesions. No history of deep abscesses, herpes simplex blistering lesions, or molluscum.
- Previously breast fed. The patient avoids milk and egg in his diet.
- Previous allergy skin tests were positive to milk, egg, and cat.

Family history:

- Mother has history of hay fever and asthma.

Environment:

- Lives in a 110-year-old house in Denver, CO. Two cats were removed from the house two months ago. There is carpeting in home, but there is no history of water damage, evaporative cooler use, or mold contamination.

Physical examination: Active, well-developed child with eczematous red, indurated lesions on his face, neck, and flexor surfaces of his arms and legs. The scalp, trunk, and diaper area are not involved. He has a few dry excoriated lesions but no pustules or vesicles. Normal hair and nails.

Laboratory Data:

- ImmunoCAP assay: egg-specific IgE 3 kUa/L, milk-specific IgE 20 kUa///L; total serum IgE = 25,000 IU/ml

Assessment: Moderate to severe AD with h/o superficial skin infection, sensitized to common food allergens and cat.

Recommendations:

- Increase baths to twice daily
- Mometasone 0.1% ointment daily to areas of severe eczema on extremities
- Desonide 0.05% ointment twice daily to eczema on face and to areas of mild eczema on neck and extremities
- Replace lotion with moisturizing cream or ointment applied twice daily to clear areas after baths and to entire body between treatments
- Sedating antihistamine at bedtime
- Avoidance of egg and milk protein
- Cat avoidance indoors

Follow-up and Discussion:

The child returns after 2 weeks. His mother reports significant improvement of the eczema on his face, neck, and extremities. Parent expressed concerns about long-term use of topical corticosteroids. Otherwise, the patient is scratching less and now is sleeping through the night. His mother wonders about milk and egg allergies, as the child recently ate cake made with egg and did not appear to have any reaction.

Examination: Mild eczematous rash on face and a few mild patches on popliteal and antecubital region. No excoriated or weeping lesions.

After discussing treatment options, the child was prescribed pimecrolimus 1% cream to be applied to all areas of eczema. Baths were decreased to once daily. Moisturizing cream was continued. After 3 weeks, his mother reports total clearing of all eczema and was able to transition the child to moisturizers alone. The child then underwent incremental food challenges in a supervised medical setting. He tolerated egg protein, but he developed an urticarial rash 15 minutes after consuming 2 grams of milk protein. His mother was advised to continue avoiding milk protein in his diet, but that egg could be reintroduced into his diet. She was also instructed to observe for respiratory symptoms suggestive of asthma given his increased risk.

Weeping and crusting may be present in more severe or infected cases. Generalized dryness is common. The childhood phase occurs from age 2 years to puberty. The flexural surfaces of the extremities are the major sites of predilection, with the antecubital and popliteal fossae most typically affected. Other frequently involved skin areas include the neck, wrist, ankle, and the creases between the thighs and buttocks. As in the infantile phase, skin lesions are often ill-defined, scaly, erythematous patches. Lichenification (an accentuation of skin markings associated with thickening of the skin) becomes a prominent feature with chronic eczema and tends to be most evident at the wrists, elbow, knees, and ankles. Although most children outgrow their AD, almost all patients have persistent dry skin and some patients continue to have AD in adulthood or, in a minority of cases, experience onset after puberty. The adult form generally involves the flexural areas of the extremities and can be focal, but in some patients, involvement will be more diffuse with large body surface areas affected. Additionally, chronic hand and foot dermatitis become prominent clinical features in adolescents and adults and may be the only manifestation of AD for some patients. Neck and facial involvement also tends to be more prominent than in the childhood phase, and patients with severe skin disease frequently have eyelid dermatitis.

The diagnosis of AD is based on 3 major features: pruritus (itchiness), an eczematous dermatitis that fits into a typical distribution as described above, and a chronic or chronically relapsing course. The majority of such patients will have a personal or family history of asthma, hay fever, or allergic rhinitis. Minor features that may help in the diagnosis include an early age of onset, dry skin, and a propensity for superficial skin infections. Laboratory tests have limited utility in diagnosing AD but can be helpful in identifying allergies that could trigger AD in a subset of patients.

What Causes AD?

The answer to this question is not completely understood but is an active area of research at National Jewish. Recent studies indicate that patients with AD, particularly individuals with more severe AD, have a null mutation in genes that encode skin barrier proteins, such as filaggrin. The lack of key skin barrier proteins makes the skin more permeable and enhances allergic sensitization. Interestingly, patients with the filaggrin null mutation frequently develop asthma in later childhood. It is likely that interactions between the host's environment, impaired skin barrier function, and immunologic factors contribute to the development of AD. Mechanisms underlying AD are reviewed in references cited at the end of this article. An understanding of these various factors is essential before mechanism-based therapies can be developed for treatment of AD.

Triggers of AD

Skin hyperreactivity is an important feature of AD. Changes in the environment, which might not affect normal individuals, can trigger the itch sensation in patients with AD and set off the itch–scratch cycle resulting in a flare of eczema. This has its parallel in the airway hyperreactivity that leads to wheezing in asthma. Eliminating known triggers of eczema is an important part of managing eczema: the more a patient scratches, the worse the eczema will become.

Irritants

A variety of factors can irritate atopic skin. Dry atopic skin is more brittle and prone to cracking, creating portals of entry for irritants, allergens, and microbes into the deeper layers of skin. Wind, low humidity, cold temperature, excessive washing without use of moisturizers, and exposure to harsh, drying soaps frequently cause this irritation.

The reason that patients with AD are so sensitive to their environment is complex. An important step in managing AD is to reduce skin irritation, which decreases the urge to scratch or rub the skin. Strategies to reduce the itching include a number of practical pearls. Patients should be taught to apply moisturizer whenever the skin feels dry or itchy. They should wash all new clothes before wearing to remove formaldehyde and other irritating chemicals, add a second rinse cycle to ensure removal of residual laundry detergent, avoid detergents that contain perfume or dye, and change to a liquid or milder detergent. It may be more comfortable to wear garments that allow air to pass freely to the skin. In addition to cotton clothing, new skin-soothing clothing lines like DermaSmart that contain antimicrobial silver may be well-accepted by patients. Working and sleeping in comfortable surroundings with a fairly constant temperature and humidity level is more comfortable. Keeping fingernails very short and smooth helps to prevent skin damage due to scratching. Use of sedating antihistamines at bedtime may reduce itching sensation to some degree through tranquilizing and sedative effects. Patients should also be instructed to use sunscreen with an SPF of 15 or higher on a regular basis and avoid getting sunburned. Sunscreens made for the face are often less irritating than regular sunscreens and products such as Vanicream sunscreen appear to be well accepted by patients with AD. Residual chlorine or bromine on the skin after swimming in a pool or hot tub may be irritating, although swimming can be a beneficial activity for atopic patients. Teaching patients to shower or bathe immediately after swimming with a mild cleanser to remove residual chemicals on the skin, then applying a moisturizer can make swimming both an enjoyable and therapeutic activity.

Allergens

Controlled allergen challenges have demonstrated that foods and inhalant allergens can trigger AD. However, it is important to realize that positive allergy skin or blood tests do not necessarily identify clinically relevant allergy. Proper allergy testing and challenges must be conducted in a controlled environment with appropriate supervision to determine which allergens flare eczema. Care must be taken to avoid only proven allergens, as it is important to avoid unnecessarily restricted diets or activities. The most common food culprits are milk, egg, peanut, soy, wheat, and fish. Environmental allergens such as dust mites and animal danders can also trigger AD. Physicians using serum IgE-specific allergen tests need to be aware that very high serum IgE levels often seen in AD can result in false-positive IgE tests for specific allergens. If food allergy is suspected, controlled food challenges, which are routinely performed in the Pediatric Care Unit at National Jewish, can be very helpful. When chemicals are suspected allergens, patch testing may be useful in the evaluation.

Infectious Agents

Bacterial infections. Bacterial skin infections can exacerbate AD. *Staphylococcus aureus* is found on the skin of most patients with AD. In contrast, less than 5% of normal subjects have *S aureus* on their skin, although it is not uncommon for healthy subjects to have *S aureus* cultured from their nares.

Research at National Jewish has found that 1 mechanism by which *S aureus* enhances skin inflammation in AD is the secretion of toxins, which behave as superantigens and markedly activate large numbers of T cells and other immune cells in the skin. Interestingly, AD patients

colonized with *S aureus* often make IgE antibodies directed against staphylococcal superantigens, suggesting that these toxins can act as allergens that persistently stimulate allergic reactions in atopic skin. Indeed, the presence of IgE antibodies to superantigens has been found to correlate with AD skin disease severity. In addition to acting as allergens, superantigens induce corticosteroid resistance of T cells, which suggests that several mechanisms exist by which superantigens increase AD severity. These studies may explain the clinical observation that in poorly controlled, superinfected AD, combined treatment with anti-staphylococcal antibiotics and topical corticosteroids is more effective than use of topical corticosteroids alone in controlling skin inflammation. On the other hand, increased binding of *S aureus* to atopic skin is related to increased expression of proteins such as fibrinogen and fibronectin in inflamed skin lesions. Treatment with anti-inflammatory medications such as topical corticosteroids or calcineurin inhibitors reduces *S aureus* counts on atopic skin. Scratching likely enhances *S aureus* binding by disturbing the skin barrier and exposing extracellular matrix molecules in the skin that act as adhesins for *S aureus*.

Compounding the problem, skin affected by AD has also been found to be deficient in antimicrobial peptides needed for host defense against bacteria and viruses. Thus, *S aureus* not only binds avidly to AD, as compared to normal skin, but, once the *S aureus* attaches to the skin of AD patients, an inadequate skin host defense also allows bacteria to grow and predispose patients to microbial infection.

Viral Infections. AD is associated with an increased propensity toward severe skin viral infections, especially Herpes simplex. This can result in eczema herpeticum, also known as Kaposi's varicelliform eruption. Molluscum contagiosum, a poxvirus infection, and warts can also be significant clinical problems in patients with AD.

The viral complications of AD have attracted much worldwide attention because smallpox vaccination of these patients or even exposure to vaccinated individuals may cause a severe widespread skin rash called eczema vaccinatum (***see Call box 1***), similar in appearance to eczema herpeticum. This propensity to eczema vaccinatum persists even after patients have outgrown AD. Due to the large number of patients with active AD or history of previous AD, this has become an impediment to mass smallpox vaccination of the general public. The mechanisms underlying this propensity for viral infections in patients with AD are actively being investigated at National Jewish and likely relate to defects in innate and adaptive immune responses.

Emotional stress. Patients with AD frequently have enormous problems with self-image and self-esteem. Anxiety and anger are also commonly experienced. Their abnormal-looking skin interferes with peer-group relationships, and the sleep disturbance that accompanies this illness is a continuous source of stress for the family. Embarrassment and frustration produce flushing, which occurs as the result of increased blood flow to the skin. Flushing not only causes erythema but also brings inflammatory cells to the local tissues. Finally, recent studies indicate that stress can cause the activation of immune cells that control skin inflammatory responses. Strategies to help minimize stress include learning about the disease as it is important to understand the long-term course of this disease; having family members learn about the disease so they can be supportive is very helpful. Many people find it useful to talk to a counselor to receive additional support or therapy. Behavioral modification or biofeedback may help with chronic itching and scratching. Patient support organizations can be helpful.

Keys to Successful Treatment of AD

Successful management requires an accurate diagnosis, adequate hydration of the skin, control of pruritus and infections, appropriate use of topical anti-inflammatory medications, and identification and elimination of exacerbating factors such as irritants and allergens. To increase the chances of successful therapy, patients and their caregivers need to be educated about the fundamentals of the disease. In addition, impact of illness on patient and family quality of life needs to be considered. Treatment should be individualized according to the severity of illness and factors that trigger their AD.

Patient Education

Learning about the chronic nature of AD, its exacerbating factors, and appropriate treatment options is important for both patients and family members. Whether a patient has had AD for months or years, it is

CALL-BOX I: Propensity to Infection Complicates Management of Atopic Dermatitis

More than 90% of patients are colonized with *Staphylococcus aureus*. Generally this can be managed with antibiotics and intensified anti-inflammatory therapy. However, viral infections can be devastating and are a complication of atopic dermatitis (AD) being actively investigated at National Jewish, thanks to research grants supported by the National Institutes of Health (National Institute of Allergy and Infectious Diseases [NIAID] and National Institute of Arthritis and Musculoskeletal and Skin Diseases [NIAMS]).

The Atopic Dermatitis and Vaccinia Network (ADVN) is a group of top medical centers, with Dr. Donald Leung at National Jewish as the principal investigator, that will be conducting clinical research studies designed to reduce the risk of viral skin infections and make smallpox vaccination safer for people with AD. The studies are sponsored by the National Institutes of Health/NIAID. People with AD are prone to increased viral skin infections such as herpes; molluscum contagiosum; and eczema vaccinatum (EV), which is a severe and potentially deadly complication of smallpox immunization that occurs almost exclusively in people with a history of AD. EV develops when AD patients are given the smallpox vaccine or come into contact with people who recently received the vaccine. Because of this, patients with AD and the people they live with do not receive smallpox vaccine. Currently, it is estimated that close to 50% of the population is ineligible for vaccination. Government officials fear the smallpox virus could be used as a weapon, making smallpox vaccination necessary. In the case of an actual smallpox outbreak, tens of millions of people could potentially receive vaccine. Studies conducted by ADVN investigators over the next 5 years will lead to a better understanding of why AD patients are prone to increased skin infections and will find safer ways to protect AD patients and their families from the threat of smallpox.

Investigators are particularly interested in enrolling patients with eczema herpeticum and a history of eczema vaccinatum. For further information, please call ***Judy Lairsmith at 303-270-2413.***

important they understand that, at present, treatment is about levels of control, not a cure. Factors including severity of disease, age, patient history, and current environment all need to be considered. Clinicians need to provide verbal and written information that includes detailed skin-care recommendations, as well as general skin-care information (***see Call-box 2***). Often, patients or parents will forget or confuse the skin-care recommendations given them without the written materials. Written instructions should be reviewed and modified at follow-up visits. Direct demonstration of skin-care techniques is very helpful and oftentimes reveals previous compliance issues. The patient or parent needs to demonstrate an appropriate level of understanding to ensure a good outcome. Patients who are "failing" conventional therapy frequently benefit from hospitalization or intense supervision. Often, removal from environmental allergens or stressors, appropriate education, and assurance of compliance with therapy result in a sustained improvement of AD.

When patients with AD have suboptimal responses to prescribed therapy, they are often prescribed another medication without attempts to evaluate the basis for poorly controlled AD. After several such encounters, patients may seek help elsewhere or are labeled as therapeutic failures. The experience at National Jewish is that the vast majority of patients labeled as having treatment failures or given a diagnosis of recalcitrant AD can be helped with conventional therapy when appropriate attention is given to the individual patient and a regimen of care is delineated and adequately taught. Realistic expectations should be set and a clear message should be given with the explanation that, at present, treatment is directed at controlling the disease, not curing it.

Basic Skin Care

Hydration

Xerosis contributes to the development of epithelial microfissures and cracks, which favors the entry of microbial organisms, irritants, and allergens. Atopic skin shows enhanced transepidermal water loss associated with impaired function of the skin's normal water permeability barrier. Patients also have decreased ceramide levels in their skin, which results in reduced water binding capacity, higher transepidermal water loss, and decreased water content. Good daily skin care that emphasizes hydration remains a cornerstone to a successful treatment plan. At the authors' center, "soak and seal" steps are central to proper skin care that emphasizes hydration, moisturization, and maintenance of an intact skin barrier. Unfortunately, some clinicians have confused this "soak and seal," which produces rehydration in conjunction with sealing in the moisture, with wetting of skin, which is typically followed by evaporation and microfissuring with soaking of skin. Thus, water avoidance is often mistakenly recommended even for patients with severe xerosis. Proper bathing or soaking the affected area should be done at least once per day for approximately 10 to 15 minutes in warm water. The involved areas should be covered to avoid evaporation. Showers may be appropriate in patients with mild disease. Water temperature should feel comfortable to the patient, as the oft-recommended "tepid" is usually too cool for most patients. Adding age-appropriate toys will help young children cooperate with the bath. Bathing may also remove allergens from the skin surface and reduces colonization by *S aureus*. A wet washcloth or towel can be used for hydration of the face or neck. Cutting out eye and mouth holes allows older patients to read or engage in other tub-safe activities. A basin can be used for eczema of the hands or feet. Baths can be increased to several times daily during flares of atopic dermatitis. Additives to the bath water have been controversial. Addition of oatmeal to the bath water may be soothing to patients but does not promote skin hydration.

CALL-BOX 2: Helpful Hints for Patients with Atopic Dermatitis

Atopic dermatitis (AD), or atopic eczema, is a chronic, recurring skin disorder which results in dry, easily irritated, itchy skin. There is no cure for AD but good daily skin care is key to controlling the disease. Because your skin is dry, understand the reasons and practice the basic principles of "soak and seal" to achieve good skin care daily.

Recommendations for Good Daily Skin Care: Soak and Seal

1. Take at least 1 bath or shower per day; use warm water, for 15–20 minutes.
2. Use a gentle cleansing bar or wash such as Dove, Oil of Olay, Eucerin, Basis, Cetaphil, Vanicream, Aveeno, CeraVe, or Oilatum. During a severe flare, you may choose to limit the use of cleansers to avoid possible irritation. Avoid scrubbing your skin with a wash cloth.
3. Pat away excess water and immediately (within 3 minutes), after the bath or shower, apply the moisturizer or the special skin medications prescribed onto **damp** skin. This will seal in the water and make the skin less dry and itchy.
4. Apply the moisturizer everywhere on skin that has not received medication. Vaseline is a good occlusive preparation to seal in the water; however, it contains no water so it only works effectively after bathing. Recommended fragrance-free moisturizers include Aquaphor Ointment, Eucerin Crème (Original or Calming), Vanicream, Cetaphil Cream, or CeraVe Cream. Moisturizers should not be applied over the medications.

Reduce Skin Irritation.

1. Wash all new clothes before wearing them. This removes formaldehyde and other potentially irritating chemicals that are used during production.
2. Add a second rinse cycle to ensure removal of soap, if you are concerned. Residual laundry detergent, particularly perfume or dye, may be irritating when it remains in the clothing. Changing to a liquid or fragrance-free, dye-free detergent may also be helpful.
3. Wear garments that allow air to pass freely to your skin. Open weave, loose-fitting, cotton-blend clothing may be most comfortable.
4. Work and sleep in comfortable surroundings with a fairly constant temperature and humidity level.
5. Keep fingernails very short and smooth to help prevent damage due to scratching.
6. Appropriate use of sedating antihistamines may reduce itching to some degree through their tranquilizing and sedative effects.

Developed by Noreen Nicol, RN, MS, FNP, Mark Boguniewicz, MD, and Donald Leung, MD, PhD; Atopic Dermatitis Program, National Jewish Medical and Research Center, Denver, Colorado.

Excellent resources for people with eczema are:

National Eczema Association for Science and Education

4460 Redwood Hwy., Ste. 16-D
San Rafael, CA 94903-1953
415.499.3474 / 800.818.7546
www.nationaleczema.org

National Jewish Medical and Research Center

1400 Jackson Street
Denver, CO 80206
1.800.222.LUNG
www.nationaljewish.org

Bath oils may give the patient a false sense of lubrication and can make the tub slippery and therefore a potential danger. The addition of bleach to bath water can be beneficial to patients with recurrent staph infections; however, the amount and frequency have not been well established. Bleach has known irritant effects, and this technique needs to be considered.

Cleansers

Cleansers with minimal defatting activity and a neutral pH are preferred. Formulations that are dye-free and fragrance-free are less irritating and more appropriate for atopic skin. They include Dove Sensitive Skin Formula, Oil of Olay, Vanicream, Basis, Cetaphil, Aveeno, CeraVe, or Oilatum. Antibacterial cleansers such as Lever 2000 may be helpful for patients with frequent folliculitis or recurrent skin infections. Patients should be instructed not to scrub with a washcloth.

Moisturizers

Recommending the use of moisturizers together with hydration may help re-establish and preserve the skin barrier. After hydrating the skin, patients should be instructed to gently pat away excess water with a soft towel and *immediately* apply moisturizer to prevent evaporation. Moisturizers are available in ointments, creams, lotions, and oils. In general, ointments are formulated with the fewest additives and are the most occlusive, and, when used following a bath or shower, they are the most hydrating. However, in a hot, humid environment, ointments may trap perspiration and increase pruritus. Lotions contain more water than creams and may have a drying effect due to evaporation. Thus, creams are preferred over lotions to increase moisturization. Although oils may go on easily, they are often much less effective moisturizers. Products may be irritating due to added dyes, fragrances, and preservatives. Preferred products are fragrance free, dye free, and contain limited preservatives. Of note, even young patients can be taught to apply their moisturizer, which allows them to participate in their skin care.

Moisturizers should be applied routinely and not over the medications. Specific occlusives or moisturizers should be individually recommended. Vaseline is a good occlusive preparation to seal in the water; however, it contains no water so it only works to seal and hydrate skin effectively after a soaking bath. Recommended moisturizers include Aquaphor Ointment, Vanicream, Eucerin Crème (Original or Calming), Cetaphil Cream, or CeraVe Cream. Several new moisturizing products have come to market that contain ceramides (eg, CeraVe and Tri-Ceram), which have been shown to be reduced in atopic skin. In addition, 2 new nonsteroidal creams (Atopiclair and MimyX) marketed as medical devices, thus requiring a prescription, have been shown to have anti-pruritic, moisturizing, as well as anti-inflammatory properties. These new products do not have any age or time usage restrictions.

Moisturizers work best when applied to skin immediately after bath or shower, but they should also be used throughout the day whenever the skin feels dry or itchy. Moisturizers should be available through local pharmacy or grocery stores and should be ordered in large (ideally 1-pound) jars or large tubes (120–180 grams). Buying moisturizers in large containers may be economically helpful to the patient, as these products need to be applied multiple ti\mes each day on a long-term basis.

Topical anti-inflammatory agents

Corticosteroids. Topical corticosteroids are frequently used for control of acute exacerbations of AD. For long-term control, once-daily use is preferred, although the data for this, as well as for maintenance therapy, come from studies with topical fluticasone or mometasone. Despite having frequent flares, many patients or caregivers do not use or delay use of topical corticosteroids due to concerns about possible adverse effects. Side effects from topical glucocorticoids are related to the potency ranking of the compound and the length of use, site of application, type of vehicle, and other factors, so it is incumbent on the clinician to instruct the patients carefully on proper use. The Practical Allergy (PRACTALL) guidelines address a number of therapeutic issues in a step-wise fashion. (PRACTALL is a collaborative effort between the American Academy of Allergy, Asthma and Immunology [AAAAI] and the European Academy of Allergology and Clinical Immunology [EAACI] to explore and recommend action on important practical issues in the field of allergy and immunology.)

Calcineurin Inhibitors: The approval of the topical calcineurin inhibitors (TCIs), tacrolimus ointment (0.03% and 0.1%), and pimecrolimus cream 1%, as nonsteroidal agents for the treatment of AD has represented a milestone in the management of AD. Both drugs have proven to be effective with a good safety profile for treatment up to 4 years with tacrolimus ointment and up to 2 years with pimecrolimus cream. A fairly common side-effect with TCIs is a transient burning sensation of the skin, although some patients may report more prolonged burning or stinging. Since treatment with TCIs is not associated with skin atrophy, these inhibitors are particularly useful for treating eczema on the face, intertriginous regions, and atrophied skin. Use of tacrolimus ointment was shown to be associated with decreased colonization by *S aureus*. Importantly, ongoing surveillance has not shown any trends towards increased frequency of viral infections especially eczema herpeticum or problems with responses to childhood vaccinations.

Currently, tacrolimus ointment 0.03% is approved for intermittent treatment of moderate-to-severe AD in children aged 2 years and older, tacrolimus ointment 0.1% for intermittent treatment of moderate-to-severe AD in adults, and pimecrolimus cream 1% is approved for intermittent treatment of patients aged 2 years and older with mild-to-moderate AD. Although there is no evidence of a causal link between cancer and the use of TCIs, the United States Food and Drug Administration has issued a "black box" warning for tacrolimus ointment 0.03% and 0.1% (Protopic, Astellas Pharma US, Inc, Deerfield, IL) and pimecrolimus cream 1% (Elidel, Novartis Pharmaceuticals Corporation, East Hanover, NJ) because of a lack of long-term safety data. (See US package inserts for Protopic and Elidel.) The new labeling also states that these drugs are recommended as second-line treatments and that their use in children younger than 2 years is currently not recommended. Of note, a Joint Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology reviewed the available data and concluded that the risk/benefit ratios of tacrolimus ointment and pimecrolimus cream are similar to those of most conventional therapies for the treatment of chronic relapsing eczema. In a recent case-controlled study of a large database that identified a cohort of 293,253 patients with AD, no increased risk of lymphoma was found with the use of TCIs.

Long-term safety studies with TCIs in patients with AD, including infants and children, are ongoing. Several studies have shown that pimecrolimus cream 1% is well tolerated and effective in infants age 3–23 months with AD. Given the chronic and relapsing nature of atopic dermatitis, the question of whether treatment of early signs or symptoms of disease with a topical calcineurin inhibitor could influence long-term

outcomes was addressed in clinical trials up to 1 year in duration with pimecrolimus cream 1%. The primary efficacy parameter was the incidence of flares and need for topical corticosteroid rescue. In the infant study, 64% of patients treated with pimecrolimus cream 1% compared to 35% of vehicle-treated patients did not require any topical corticosteroids during the study. In addition, subgroup analysis showed that there were significantly fewer flares in children of all clinical severities, including those with severe AD in the group treated with pimecrolimus cream 1%. These studies suggest that earlier use of a topical calcineurin inhibitor can lead to better long-term disease control with fewer flares and significantly less need for topical corticosteroid rescue therapy. Finally, a long-term study of a group of over 1000 infants with AD enrolled between ages 3–18 months and treated with either pimecrolimus cream 1% or conventional therapy is currently in its third year. This cohort is unique in that patients were enrolled within 3 months of being diagnosed with AD and without any signs of asthma or allergies. Impact of the 2 treatment interventions on AD is the primary outcome for the first 3 years of the study, while incidence of asthma at age 6 years will be the primary outcome for the second phase of the study.

Identification and elimination of allergens

Potential allergens can be identified by taking a careful history and carrying out selective allergy tests. Negative skin-prick tests or serum tests for allergen-specific IgE have a high predictive value for ruling out suspected allergens. Positive skin or in vitro tests for IgE to allergens, particularly to foods, may not correlate with clinical symptoms and should be confirmed with controlled food challenges, elimination diets, or atopy patch test. Avoidance of foods implicated in controlled challenges can result in clinical improvement. As a rule, extensive elimination diets, which in some cases can be nutritionally deficient, should be avoided. Most food-allergic children outgrow their food hypersensitivity to the majority of food allergens in the first few years of life, making it less relevant as a trigger in older patients. Prolonged avoidance of house dust mites in sensitized AD patients has been found to result in improvement of their skin disease. Avoidance measures include use of house dust mite-proof encasings on pillows, mattresses, and boxsprings; weekly washing of bedding in hot water; removal of bedroom carpeting; and decreasing indoor humidity levels.

Management of skin infection

Honey-colored crusting, extensive serous weeping, folliculitis, and pyoderma indicate bacterial skin infection usually secondary to *S aureus* overgrowth in patients with AD. These patients can have a sudden exacerbation of their skin disease and respond rapidly to antibiotic therapy. Topical mupirocin offers some utility in the treatment of localized impetiginized lesions. In patients with extensive superinfection with sensitive *S aureus* strains, a course of systemic antibiotics such as first-generation cephalosporins may be necessary. In patients who do not respond well to antibiotics, drug-resistant S aureus should be suspected and the organism should be cultured and tested for antibiotic sensitivities.

Due to the increased risk of bacterial antibiotic resistance accompanying frequent use of antibiotics, it is important to combine antimicrobial therapy with effective anti-inflammatory therapy. As already discussed, the excoriated inflamed skin of AD predisposes to *S aureus* colonization. Therefore, use of antibiotic therapy must be carried out with good skin hydration to restore skin barrier function and topical steroids or calcineurin inhibitors to reduce overall skin inflammation and *S aureus* colonization. In patients with superantigen-induced steroid resistance, the topical calcineurin inhibitors may have an advantage in controlling underlying skin inflammation.

AD can be complicated by recurrent viral skin infections such as warts and molluscum contagiosum. Herpes simplex, resulting in eczema herpeticum, can be a serious infection. After an incubation period of 5 to 12 days, multiple, itchy, vesiculopustular lesions erupt in a disseminated pattern; vesicular lesions are umbilicated, tend to crop, and often become hemorrhagic and crusted. The presence of punched-out erosions, vesicles, and/or infected skin lesions that fail to respond to oral antibiotics should initiate a search for herpes simplex. Antiviral treatment for cutaneous herpes simplex infections is of critical importance in the patient with widespread AD since life-threatening dissemination has been reported. In patients with AD, smallpox vaccination or even exposure to vaccinated individuals may cause a severe widespread skin rash called eczema vaccinatum similar in appearance to eczema herpeticum (***see Call-box 1***).

Patients with AD have an increased prevalence of fungal infections compared to non-atopic controls. There has been particular interest in the role of *Malassezia furfur* (*Pityrosporum ovale*) in AD. M furfur is a lipophilic yeast commonly present in the seborrheic areas of the skin and in the scalp. IgE antibodies against *M furfur* are commonly found in AD patients and most frequently in patients with head and neck dermatitis. The potential importance of *M furfur* as well as other dermatophyte infections is further supported by the reduction of AD skin severity in some patients following treatment with anti-fungal agents.

Antihistamines. Reduction of skin inflammation and dryness with topical corticosteroids or calcineurin inhibitors as well as skin care combined with elimination of allergens will often symptomatically reduce pruritus. Since histamine is only 1 of many mediators that can induce pruritus, most patients may derive minimal benefit from antihistaminic therapy. Studies of newer nonsedating antihistamines have shown variable results in their effectiveness to control pruritus although they may be useful in the subset of AD patients with concomitant urticaria.

Since pruritus is usually worse at night, sedating antihistamines, such as hydroxyzine or diphenhydramine offer an advantage when used at bedtime. Doxepin hydrochloride has both H1- and H2-histamine receptor-blocking effects. If nocturnal pruritus remains severe, short-term use of a sedative to allow adequate rest may be appropriate. Treatment of AD with topical antihistamines is not very useful and can induce cutaneous sensitization.

What To Do With The "Difficult-To-Manage" Patient

Day Hospitalization. Treating patients who are failing conventional therapy can be very frustrating for the patient, family, and clinician. Prior to prescribing more aggressive therapy, it is essential to ensure that poor control is not due either to poor adherence, or on-going exposure to triggers or misunderstandings regarding treatment recommendations. This may require hospitalization or a day program to evaluate potential confounding factors in the management of poorly controlled AD. Additionally, patients who are erythrodermic or have very widespread skin disease that is unresponsive to outpatient therapy often benefit from hospitalization before experimental therapies or therapies with significant potential side-effects are initiated.

Hospitalization also removes the patient from allergens in the home

and allows time for intensive education and supervised topical care. It assures the physician of adherence with the prescribed treatment regimen. Hospitalization may also be used for provocative challenges to identify specific allergic triggers. The psychosocial aspects of this chronic relapsing disease can be addressed, including habitual scratching and sleep disturbances. Patients commonly improve during hospitalization, avoiding the need for more aggressive therapies. National Jewish Medical and Research Center has a team of nationally and internationally recognized experts who use an interactive, multi-disciplinary, team approach to evaluate and intensely treat patients with AD who fail outpatient management (***see Call-box 3***).

Wet Dressings. Wet dressings can be used on severely affected or refractory lesions, and the technique should be taught carefully in a controlled setting. Of note, wet wrap therapy for the treatment of atopic dermatitis has been successfully used at National Jewish for more than 2 decades. It has become an important add-on therapy for severe disease. Dressings may serve as an effective barrier against persistent scratching, allowing more rapid healing of excoriated lesions (***see Figure 1***) and enhance skin hydration. Hydration promotes penetration of topical medications into the skin, which increases the amount of medication deposited in the areas of inflammation.

Wet wrap dressings also reduce pruritus and act as a protective barrier from the trauma associated with scratching. Wet dressings are particularly helpful for limited areas of recalcitrant dermatitis, such as the hands or feet, and are generally used for a short period of time, such as 3 to 5 days. Wet dressings are reported to cause maceration of the skin, folliculitis, and secondary infection if overused, and may promote skin dryness if sufficient emollients are not part of the regimen. These are uncommon in the authors' experience when used properly. In fact, *S aureus* colonization was found to be decreased in a recent controlled study of wet wrap dressings with topical corticosteroid. However, we do agree this therapy is probably best reserved for acute, severe exacerbations of AD. It can also be used selectively to limited areas of resistant dermatitis with minimal inconvenience. Wet wraps should not be used on a routine basis or part of daily normal skin care.

The standard method involves soaking the patient in bath water, rapidly applying topical corticosteroids or other topical medications to inflamed areas, then placing water-soaked cloth dressings, such as Kerlex or cotton clothing, over the areas, followed by an outer layer of dry cloth dressings or cotton clothing. They should always be used in conjunction with topical medications or moisturizers. Healthcare providers should be aware that the package inserts and patient instructions state that medications like topical calcineurin inhibitors under occlusion, which may promote systemic exposure, has not been evaluated (pimecrolimus) or should not be used with occlusive dressings (tacrolimus). Wet dressings are an effective treatment for recalcitrant eczema, but it is imperative patients be closely supervised by a physician with expertise in their use.

Emotional Stressors. AD patients often respond to frustration, embarrassment, or other stressful events with increased pruritus and scratching that triggers the scratch–itch cycle thereby aggravating their skin disease. The impact of AD on quality of life extends to the parents, extended family, the school system, and even the future work environment of these individuals. AD is an important cause of school absenteeism, as well as occupational disability, and the difficulties associated with chronic AD are not borne solely by the patient. All healthcare providers must recognize the potential need to treat depression and other psychosocial issues commonly seen in patients with AD and their families. Anger and anxiety are common in caregivers who attend to an affected child. For example, one should never underestimate how difficult it might be for a mother who cannot sleep because of caring for a nonsleeping child to function at

CALL-BOX 3: National Jewish Medical and Research Center Is A Center of Excellence for the Management of Atopic Dermatitis

National Jewish Medical and Research Center has a team of experts recognized nationally and internationally for their work in atopic dermatitis (AD). Patients treated at National Jewish benefit from our interactive, multidisciplinary, team approach. This team is composed of physicians specializing in pediatric allergy and immunology, nurse specialists, dietitians, rehab staff, child-life workers, psychologists, and psychiatrists. Our philosophy of care for patients is for comprehensive evaluation and treatment that fits the needs and goals of the patient. At National Jewish, we provide single-day consultations, multi-day outpatient visits, or inpatient care for more extensive testing and treatment. In the multi-day outpatient visit program or as an inpatient, patients who are "failing" conventional therapy frequently benefit from hospitalization or intense supervision. When a patient has had AD for months or years, it is important they understand that treatment is about levels of control, not a cure.

National Jewish has the expertise in difficult diagnostic or disease management problems for AD patients. Comprehensive testing and challenges are incorporated in the multi-day stay. Teaching about the chronic nature of AD, exacerbating factors and appropriate treatment options is important for both patients and family members. Patient education classes specific to AD care as well as in depth one-on-one teaching are age-appropriate and emphasize self care. Demonstrated techniques for selfcare, including on-site tub baths and the application of topical medications and wraps is key. Direct observation of skin care techniques patients use is very helpful and oftentimes revealing as to previous compliance issues. The patient or parent needs to demonstrate an appropriate level of understanding to ensure a good outcome. Often, removal from environmental allergens or stressors, education, and assurance of compliance with therapy results in a sustained improvement of the AD. Customized home-care instructions as well as general disease information are provided to the patient and family on discharge. Treatment for children, adolescents, and adults with AD is viewed as a partnership between the patient/family, primary physician, and the AD team.

National Jewish also offers free booklets, instruction sheets, and program brochures specifically on atopic dermatitis available through Lung-Line at 1-800-222-LUNG or the web site at www.nationaljewish.org. Understanding and addressing each patient's expectations of disease control are key for success.

an acceptable level during normal waking hours. Indeed, it has been reported that caring for a child with AD is more stressful than caring for someone with insulin-dependent diabetes. Efforts should be made to identify sources of stress including marital separation and teasing from peers or siblings. Psychological evaluation or counseling should be considered in patients who have difficulty with emotional triggers or psychological problems contributing to difficulty in managing their disease.

Relaxation or biofeedback may be helpful in patients with habitual scratching. In situations in which stress triggers increased scratching, behavior modification can be useful in channeling patients' scratching into more useful activities. When available, art therapy and play therapy may be helpful for such patients. In patients with excessive anxiety, depression, itching, and sleep difficulties, psychotropic drugs may be required. In some patients, depression can interfere with their ability to follow a skin-care routine. Such individuals may benefit from treatment with antidepressant drugs such as tricyclics or specific serotonin reuptake inhibitors. In patients with poorly controlled AD, psychiatric referrals should be considered not only for pharmacologic intervention but also to identify situations and patterns of behavior that are stressful and trigger flares of AD.

Phototherapy. Natural sunlight is frequently beneficial to patients with AD. However, if the sunlight occurs in the setting of high heat or humidity, thereby triggering sweating and pruritus, it may be deleterious to patients. Broadband ultraviolet B (UVB), broadband ultraviolet A (UVA), narrow-band UVB (311 nm), UVA-1 (340-400 nm), and combined UVAB phototherapy can be useful adjuncts in the treatment of AD. Photochemotherapy with PUVA should be restricted to patients with severe, widespread AD, though studies comparing it with other modes of phototherapy are limited. Short-term adverse effects with phototherapy may include erythema, skin pain, pruritus, and pigmentation. Potential long-term adverse effects include premature skin aging and cutaneous malignancies.

Systemic corticosteroids. The use of systemic glucocorticoids, such as oral prednisone, is rarely indicated as the clinical improvement is frequently followed by a severe rebound flare after discontinuation. Short courses of oral glucocorticoids may be appropriate for an acute exacerbation while other treatment measures are being instituted. In this case, it is important to taper the dosage and begin intensified skin care, particularly with topical glucocorticoids and bathing followed by application of emollients, in order to prevent rebound flares.

Cyclosporine. Cyclosporine is a potent immunosuppressive drug that acts primarily on T cells by suppressing cytokine transcription. The drug binds to intracellular cyclophilin and thereby acts similarly to tacrolimus and pimecrolimus. Studies have demonstrated that both children and adults with severe AD, refractory to conventional treatment, can benefit from short-term cyclosporine treatment with improved quality of life. However, discontinuation of treatment may result in relapse. Elevated serum creatinine or more significant renal impairment and hypertension are specific side effects of concern.

Other Therapies. Intravenous immunoglobulin has been reported to be beneficial in patients with refractory AD, primarily children, although controlled studies are lacking. Recombinant human interferon-gamma has also been shown to be of benefit in select refractory AD patients. Anti-metabolites such as mycophenolate mofetil (CellCept), azathioprine and methotrexate have also been used in limited numbers of patients. Due to potential serious toxicities, these should be instituted by physicians with expertise in this area. Omalizumab (anti-IgE) has been reported to be of benefit in AD in only isolated cases to date. Allergen desensitization (allergy shots) are currently not indicated for AD, although several recent European studies of adults with chronic AD who are allergic to dust mites suggest clinical efficacy. In the authors' experience, many patients undergoing allergy desensitization for allergic rhinitis or asthma report flaring of their AD with injections.

How Can National Jewish Help?

AD can be very difficult to live with. Each person with AD deserves to learn what makes their symptoms worse, how to avoid them, and how to best treat them. This is different for each individual. National Jewish is 1 of the leading institutions in the United States for treatment and research of AD (***see Call Box 3***). Patients treated at National Jewish benefit from our interactive, multi-disciplinary, team approach. Our philosophy of care for patients is for comprehensive evaluation and treatment that fits the needs and goals of the patient. At National Jewish, we provide single-day consultations, multi-day outpatient visits, or inpatient care for more extensive testing and treatment. If you have questions, please contact the National Jewish LUNG LINE™ at 1-800-222-LUNG.

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Accreditation Instructions

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1. Lichenification:

a. Is a prominent clinical feature only during of the adult phase of AD
b. Is most evident on the neck and face
c. Is an accentuation of skin markings associated with thickening of the skin
d. Is seen only during acute AD flares

2. Who is at risk for eczema vaccinatum?

a. Adults who have outgrown AD receiving smallpox vaccine
b. Patients with AD who are exposed to recently vaccinated individuals
c. Children who have outgrown AD receiving smallpox vaccine
d. All of the above

3. Which of the following is most consistent with proper "Soak and Seal" method of skin care for AD:

a. Bathe in tepid water for 15 minutes followed by application of moisturizer and then medication applied on top
b. Shower in warm water followed by a thorough drying of the skin and then use of moisturizer to entire body
c. Bathe in warm water followed by immediate application of anti-inflammatory medications to affected areas and application of moisturizer to uninvolved areas
d. Bathe only twice weekly followed by application of topical anti-inflammatory medications to affected areas, then application of moisturizer over the medications

4. Topical calcineurin inhibitors:

a. are a new class of steroids.
b. are indicated in children as young as 2 years of age with mild to moderate AD (pimecrolimus cream 1%) and moderate to severe AD (tacrolimus ointment 0,03%).
c. cannot be used on facial eczema.
d. use is associated with increased skin infections.

5. Wet dressings:

a. may promote skin dryness if not used with sufficient emollients
b. should not be used over topical corticosteroids
c. prevent healing of excoriated lesions
d. are not effective for patients with recalcitrant eczema

Evaluation

1. Please rate the value of the topic.
❍ Superior ❍ Excellent ❍ Good ❍ Average ❍ Fair ❍ Poor

2. Please rate the relevance to your practice.
❍ Superior ❍ Excellent ❍ Good ❍ Average ❍ Fair ❍ Poor

3. Please rate the quality of the information.
❍ Superior ❍ Excellent ❍ Good ❍ Average ❍ Fair ❍ Poor

4. Did this activity succeed in meeting its educational objectives?
❍ Yes ❍ No

5. Will this activity change the way you treat patients?
❍ Yes ❍ No ❍ Unsure

6. Please explain your answer to question 5.

_____

_____

7. Do you believe this activity contains pharmaceutical industry bias?
❍ Yes ❍ No

8. How did you hear about this program?
❍ Colleague ❍ E-mail ❍ Mailing ❍ Website ❍ Other

9. In the future, which CME topics would you like National Jewish to address? (Check all that apply.)

Pediatric Asthma: ❍ Diagnosis ❍ Treatment ❍ Management

Adult Asthma:
❍ Diagnosis ❍ Treatment ❍ Management

COPD:
❍ Diagnosis ❍ Treatment ❍ Management

Allergies:
❍ Diagnosis ❍ Treatment ❍ Management

Sleep Disorders:
❍ Diagnosis ❍ Treatment ❍ Management

Tuberculosis:
❍ Diagnosis ❍ Treatment ❍ Management

Immunologic Diseases:
❍ Diagnosis ❍ Treatment ❍ Management

Atopic Dermatitis:
❍ Diagnosis ❍ Treatment ❍ Management

Other topics:

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_____

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