

## SPECIAL EDITION

## Advances in Our Understanding and Management of Atopic Dermatitis

### INTRODUCTION

Atopic dermatitis (AD), also known as atopic eczema, is the most common chronic, relapsing skin disorder seen in infants and children. AD is associated with dry, easily irritated, itchy skin leading to scratching, disruption of sleep and reduction in quality of life. These skin symptoms can also start or persist into adulthood. This skin condition usually occurs in people who have asthma, hayfever, or food allergies or in family members of people who have these disorders. Along with asthma and allergic rhinitis, 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 one strategy to prevent the atopic march. This review will examine our current understanding of AD and effective strategies being used at National Jewish Medical and Research Center to manage this common skin disease.



Patient with severe facial atopic dermatitis.

### CLINICAL FEATURES OF AD

The onset of AD is usually during early childhood with nearly 90% of patients presenting during the first five years of life. These children will often have a family history of asthma, hay fever or food allergy. The cardinal feature of AD is significant pruritus or itching that disrupts sleep and often interferes with daily activities. The rash has three 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 often appears on the cheeks, scalp, wrists, extensor aspects of the legs, and neck. Involvement of the trunk is common but the diaper area is usually spared. Infantile AD lesions tend to be symmetric, scaly, and erythematous. Weeping and crusting may be present in more severe cases. Generalized dryness is common. The childhood phase lasts from age two to puberty. The flexural surfaces of the extremities are the major sites of predilection with the antecubital and popliteal fossae most commonly affected. Other frequently involved sites include the neck, wrist and ankle, and the creases between the thighs and buttocks. As in the **infantile phase**, skin lesions are often ill-defined, scaly, erythematous

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patches. Lichenification (an accentuation of skin markings associated with thickening of the skin) becomes a prominent feature during the childhood phase and tends to be most evident at the wrists, elbow, knees and ankles. Although many children outgrow their AD, almost all patients have persistent dry skin and some patients continue to have AD in adulthood or have their 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. 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 some patients have severe skin disease around their eyes. Older patients have more chronic findings than younger patients and dryness of their skin and lichenification are prominent findings.

The diagnosis of AD is based on three 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 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 may be helpful in select cases.

### TRIGGERS OF AD

Skin hyperreactivity is an important feature of AD. Changes in the environment, which might not affect normal individuals, can elicit the itch sensation in patients with AD and set off the itch-scratch cycle that results in a flare of eczema. This is similar to the airway hyperreactivity that leads to wheezing in asthma.

#### Irritants

A variety of factors can irritate atopic skin and cause the eczema to flare if the skin barrier is not intact. Wind, low humidity, cold temperature, excessive washing without use of moisturizers, and use of harsh, drying soaps are frequently noted to cause this irritation. The reason that patients with AD are so sensitive to their environment is complex. One important cause is that they have a defect in their skin barrier function. Certain lipids, such as

ceramides, are lacking in the stratum corneum or top layer of their skin. This results in water loss from the skin. Dry skin is more brittle and prone to cracking thus creating portals of entry for irritants, allergens and microbes into the deeper layers of skin.

#### Allergens

Controlled allergen challenges have demonstrated that foods and inhalant allergens can trigger AD. AD is often called the “itch that rashes”. This is because exposure to triggers causes the patient to feel a sensation of itch, but it is not until the patient scratches their skin that the rash actually appears. Eliminating known triggers of eczema is therefore an important part of managing eczema because the more a patient scratches the worse their eczema will become. At National Jewish, health care providers specializing in the management of AD take a careful history to identify potential allergens and do skin testing to verify that the patient is sensitized to potential allergens. The most common food culprits are egg, peanut, milk, soy, wheat and fish. Environmental allergens such as dust mites, animal dander and pollen can also trigger AD. A positive skin test to a food or environmental allergen does not always mean the patient is allergic to the substance. If food allergy is suspected, the most definitive method is the double-blind, placebo-controlled food challenge which is routinely performed in the Pediatric - Care Unit at National Jewish. Foods that have been demonstrated to flare AD in controlled challenges need to be avoided. This procedure is particularly important to carry out when a patient has multiple positive skin tests to foods and finds the diet to be too restrictive. In the latter situation, it is important to consult with a dietitian to be certain that the elimination diet that is being adhered to eliminates hidden food allergens and most importantly that the diet is still nutritious.

#### 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. Research at National Jewish has found that an important strategy by which *S. aureus* enhances skin inflammation in AD is by secreting toxins such as superantigens which stimulate marked activation of T cells and antigen-presenting 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 which persistently stimulate allergic reactions in atopic skin. Indeed, the presence of IgE antibodies to superantigens have been found to correlate with AD skin disease severity. In addition to acting as an allergen, superantigens induce corticosteroid resistance of T cells suggesting that several mechanisms exist by which superantigens increase AD severity. These studies may explain the clinical observation in poorly-controlled AD, superinfected with *S. aureus*, that combined treatment with anti-staphylococcal antibiotics and topical corticosteroids is much more effective than use of topical corticosteroids alone to control severity of skin inflammation.

The increased binding of *S. aureus* to atopic skin has been found to be secondary to underlying allergic skin inflammation. This is supported by the clinical observation that treatment with 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*, e.g. fibronectin and collagens. In studies of *S. aureus* binding to skin lesions, bacterial binding was significantly greater at skin sites with allergic inflammation. This was localized to IL-4 induced expression of fibronectin. Compounding the problem, AD skin 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 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, 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 AD, this has become an impediment to mass smallpox vaccination in the general public. The mechanisms underlying this propensity for viral infections in patients with AD is actively being investigated at National Jewish (*see Call-box 1*) and likely relates to defects in innate and adaptive immune responses.

**Emotional stress.** Patients with AD frequently have enormous problems with self-image and self-esteem. Their abnormal looking skin interferes with peer group relationships and the sleep disturbance which accompanies this illness is a continuous source of stress for the family. Embarrassment and frustration results in flushing which occurs as the result of increased blood flow to the skin, not only causing erythema, but also bringing inflammatory cells to the local tissues. Finally, recent studies indicate that stress can cause the activation of immune cells which control skin inflammatory responses.

## WHAT CAUSES AD?

The answer to this question is not completely understood but is an active area of research at National Jewish. It is likely that interactions between susceptibility genes, 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.

## 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, identification and elimination of exacerbating factors including 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.

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

Over 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 is a complication of atopic dermatitis being actively investigated at National Jewish thanks to research grants supported by the National Institutes of Health (NIAID and NIAMS).

The Atopic Dermatitis and Vaccinia Network (ADV N) is a group of top medical centers, with Dr. Leung at National Jewish as the principal investigator, that will be conducting clinical research studies designed to reduce the risk of skin infections and make smallpox vaccination safer for people with atopic dermatitis (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) 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 ADV N investigators over the next five 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 will be 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.

### Patient Education

If a patient has had AD for months or years, it is important they understand that treatment is about levels of control, not a cure. Learning about the chronic nature of AD, exacerbating factors and appropriate treatment options is important for both patients and family members. 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 disease 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 often times 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, education and assurance of compliance with therapy results in a sustained improvement of the 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 with 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 delineated and adequately taught. Realistic expectations should be set, and a clear message that at present, treatment is directed at controlling disease, not curing it.

## 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.

### Recommendations for Good Daily Skin Care! Soak and Seal

1. Take at least one 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® or Oilatum®. During a severe flare, you may choose to limit the use of cleansers to avoid possible irritation.
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 which 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 a bathing. Recommended fragrance-free moisturizers include Aquaphor® Ointment, Eucerin® Crème Original or Calming, Vanicream®, Cetaphil® Cream, or Moisturel® 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 which are used during production and packing.

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 which 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.

7. An excellent resource for people with eczema is the:

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### Basic Skin Care

Good daily skin care emphasizing hydration and maintenance of an intact skin barrier remains a cornerstone to a successful treatment plan. In AD, the disturbed skin barrier function is likely due to reduced lipid (e.g. ceramide) levels and results in dry skin (xerosis) and enhanced transepidermal water loss. Irritants such as soaps or detergents, contact with chemicals, smoke, alcohol and astringents found in toiletries as well as abrasive clothing can worsen the xerosis. Soaps with minimal defatting activity and a neutral pH are preferred. Xerosis contributes to the development of epithelial microfissures and cracks, which favors the entry for skin pathogens, irritants, and allergens. The patient education page accompanying this update outlines some specific recommendations (*Call-box 2*). Offering patients and families resources and tools to assist them with the management of their disease is important.

### Topical anti-inflammatory agents

**Corticosteroids.** Topical glucocorticoids are frequently used for control of acute exacerbation of AD. However, recent studies suggest that once control of AD is achieved with a daily regimen of topical glucocorticoid, long-term control can be maintained with twice weekly applications of topical fluticasone or mometasone to areas that have healed but are prone to developing eczema. Side effects from topical glucocorticoids are directly related to the potency ranking of the compound and the length of use, so it is incumbent on the clinician to instruct the patients and to balance the need for a more potent steroid with the potential for side effects. Therefore, ultrahigh-potency glucocorticoids should be used only for very short periods of time and in areas that are lichenified but not on the face or intertriginous areas.

**Calcineurin Inhibitors.** The non-steroidal topical calcineurin inhibitors are a new class of dermatologic drugs which are effective in reducing AD skin inflammation. Tacrolimus ointment 0.1% and 0.03% (Protopic®; Fujisawa Healthcare, Inc.) are indicated for the treatment of moderate to severe AD. Pimecrolimus cream 1% (Elidel®; Novartis Pharmaceuticals Company) is indicated for the treatment of mild to moderate AD. Both are currently approved in patients age two years and older.

The approval of topical calcineurin inhibitors for the treatment of AD represents a significant advance in our

management options for this disease. However, we must still develop guidelines for use of topical corticosteroids vs calcineurin inhibitors in the management of AD. There are situations in which topical calcineurin inhibitors may be advantageous over topical corticosteroids. These would include treatment of patients who are poorly responsive to topical steroids, patients with steroid phobia and the treatment of face and neck dermatitis where ineffective, low potency topical corticosteroids are usually used due to fears of steroid-induced skin atrophy. The potential use of topical calcineurin inhibitors as maintenance therapy is also intriguing for prevention of AD flares.

### Identification and elimination of allergens

Potential allergens can be identified by taking a careful history and carrying out selective allergy tests. Negative prick skin 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; washing bedding in hot water weekly; 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 one of many mediators that can induce pruritus, most patients may derive minimal benefit from antihistaminic therapy. Studies of newer non-sedating 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 fail conventional therapy can be very frustrating. Prior to prescribing more aggressive therapy, it is essential to ensure that poor control is not due either to poor adherence, on-going exposure to triggers or incorrect use of emollients and/or medications. This may require hospitalization or a day program to evaluate potential confounding factors in the management of poorly controlled AD. As well, patients who are erythrodermic or have very widespread skin disease unresponsive to outpatient therapy often benefit from hospitalization before experimental therapies are initiated.

Hospitalization removes the patient from allergens in the home and allows time for intensive AD education and topical care. It also assures the physician of adherence with the treatment regimen. Parenteral or oral antibiotics may be administered for secondary infection. Hospitalization may be used for provocative challenges to identify specific allergic triggers and wet wraps (*see page 9*) can be instituted. Patients commonly improve during hospitalization, avoiding need for more aggressive

therapies. National Jewish Medical and Research Center has a team of experts recognized nationally and internationally for their work in AD who use an interactive, multi-disciplinary, team approach to evaluate and intensely treat patients who fail outpatient management (*see Call-box 3*). Comprehensive testing and challenges are incorporated in the multi-day stay. Demonstrated techniques for self-care, including on-site tub baths and the application of topical medications and wraps is key.

*Wet Dressings.* Wet dressings can be used on severely affected or chronic lesions refractory to skin care. 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 corticosteroids into the skin, increasing the amount of medication deposited in the areas of inflammation. 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 may cause maceration of the skin and secondary

### 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, multi-disciplinary, 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 which 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 self-care, 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 often times 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](http://www.nationaljewish.org). Understanding and addressing each patient’s expectations of disease control is key for success.

**FIGURE 1**

① Patient with severe facial atopic dermatitis.



② Patient responds to wet wrap therapy which his mother is taught to do at National Jewish Medical and Research Center in Denver.



③ Patient after treatment.



infection if overused, and may promote skin dryness if sufficient emollients are not part of the regimen. The standard method involves soaking the patient in bath water, rapidly applying topical corticosteroids or topical calcineurin inhibitors 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. 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 an affected child. For example, one should never underestimate how difficult it might be for a mother who can not sleep because of caring for a non-sleeping child to function at 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 where stress triggers increased scratching, behavior modification can be useful in channeling their 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 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. Broad-band ultraviolet B (UVB), broad-band 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 at 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 generally results in relapse flares. Elevated serum creatinine or more significant renal impairment and hypertension are specific side effects of concern.

**Anti-metabolites.** Mycophenolate mofetil (MMF), a purine biosynthesis inhibitor used as an immunosuppressant in organ transplantation, has been used for treatment of refractory inflammatory skin disorders. Short term oral MMF 2g daily as monotherapy has been reported in open-label studies to result in clearing of skin lesions in 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*. Dose-related bone marrow suppression has also been observed. Of note, not all patients benefit from treatment. Therefore the medication should be discontinued if patients do not respond within 4-8 weeks.

Methotrexate is an antimetabolite with potent inhibitory effects on inflammatory cytokine synthesis and cell chemotaxis. It has been used for AD patients with recalcitrant disease, though controlled trials are lacking. Azathioprine is a purine analogue with anti-inflammatory

and antiproliferative effects, which has been utilized for severe AD, though no controlled trials have been reported. Myelosuppression is a significant adverse effect, and thiopurinemethyl transferase levels may predict individuals at risk. Leflunomide, a pyrimidine de novo synthesis-inhibiting immunosuppressant, has also been reported to be effective in treating severe AD.

**Other Therapies.** Intravenous immunoglobulin has been reported to reduce skin inflammation in patients with refractory AD. Several studies have also suggested that patients with AD benefit from treatment with traditional Chinese herbal therapy. The possibility of hepatic toxicity, cardiac side effects, or idiosyncratic reactions, however, is a concern. The specific ingredients of the herbs also remain to be elucidated and some preparations have been found to be contaminated with glucocorticoids.

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