

Efficacy and Safety Considerations in Topical Treatments for Atopic Dermatitis

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Atopic dermatitis (AD), often referred to as atopic eczema, is one of the most common chronic inflammatory skin diseases frequently seen in young children. Key characteristics of AD are severe dryness caused by transepidermal water loss, intense itching, and cutaneous inflammation. The clinical course of AD is cyclic, characterized by disease exacerbations, or flares, ranging from mild to severe. There is no cure for AD, which is often chronic and relapsing, thereby presenting salient challenges for the nurse, the nurse practitioner (NP), other health care providers, as well as patients and their families. Broadly stated, the goals of effective management are to reduce the symptoms of the disease and to prolong the time between flares.

Atopic dermatitis is a complex disease involving interaction among genes (Palmer et al., 2006; Weidinger et al., 2008), the external environment (Flohr et al., 2008; Proksch,

As no cure exists for atopic dermatitis, the goals of treatment include reducing symptoms and prolonging periods between flares. Proper skin care can improve skin barrier function, reducing susceptibility to triggers of flares. Topical corticosteroids and topical calcineurin inhibitors may improve symptoms.

Fölster-Holst, & Jensen, 2006), and immune dysregulation (McGirt & Beck, 2006; Ong & Leung, 2006). Breakdown of the epidermal skin barrier is recognized as a fundamental step in the pathogenesis of AD; however, it remains controversial whether barrier dysfunction is secondary to the inflammatory response to irritants and allergens ("inside-outside hypothesis") or whether the epidermal damage is responsible for disease ("outside-inside hypothesis") (Nicol & Boguniewicz, 2008). It is also possible skin barrier dysfunction may both contribute to and exacerbate the development of AD (Spergel, 2008).

Atopic dermatitis affects up to 20% of children and 3% of adults (Larsen & Hanifin, 2002). In recent decades, there has been an increase in the global prevalence of the disease, particularly among young children (Williams et al., 1999). Studies indicate AD precedes the development of other atopic diseases, including asthma, allergic rhinitis, and food allergies, a phenomenon known as "the atopic march" (Kapoor et al., 2008; Porsbjerg, von Linstow, Ulrik, Nepper-Christensen, & Backer, 2006; Spergel & Paller, 2003;

van der Hulst, Klip, & Brand, 2007). Some potential risk factors associated with the rise in AD include small family size, increased income and education, migration from rural to urban environments, and increased use of antibiotics (von Mutius et al., 2000). While the exact causes of AD are not fully understood, it is clear the disease can exert a significant burden on quality of life, and it has been linked to low self-esteem, sleep deprivation, and decreased productivity, among other debilitating psychosocial effects (Fivenson et al., 2002). The outcome of AD is very difficult to predict in any individual, but fortunately, the disease often progresses to periods of remission as the patient grows older.

Clinical Features and Diagnosis

Atopic dermatitis is divided into three phases on the basis of age and distribution of lesions: infantile, childhood, and adult. There continues to be no single distinguishing feature of AD or a diagnostic laboratory test. Laboratory testing is not needed in the routine evaluation and treatment of

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uncomplicated AD. The diagnosis is based on three major clinical features: pruritus, an eczematous dermatitis that fits into a typical distribution as described below, and a chronic or chronically relapsing course. The key feature of AD is pruritus (itchiness), which can interfere with daily activities and disrupt sleep.

In infants, AD typically presents on the cheeks, forehead, or scalp. AD lesions tend to be symmetrical, scaly, and erythematous and may remain localized or extend to the trunk or extremities. Weeping and crusting may occur in more severe or infected cases. Lesions do not usually affect the diaper area, which aids in diagnosis. General xerosis or dryness are common.

The childhood phase of AD, which can follow the infantile phase without interruption, occurs from age 2 to puberty. The exudative lesions of infancy are less likely to occur, while lichenified papules and plaques indicative of more chronic disease are usually exhibited. Typically, hands, feet, wrists, ankles, and antecubital and popliteal regions are affected. Localization at flexural areas of the extremities is more common.

The adult phase of AD usually begins at puberty, although some patients may experience onset of symptoms after puberty. Affected areas are characterized by dry, scaling, erythematous papules and plaques and the formation of large lichenified plaques resulting from chronic lesions. In adults, AD usually presents in flexural folds, the face and neck, upper arms and back, and the dorsa of hands, feet, fingers, and toes. Most children outgrow their AD but continue to have dry, easily irritated skin.

Because many inflammatory skin diseases, immunodeficiencies, infectious diseases, and infestations exhibit symptoms similar to AD, many differential diagnoses must be ruled out, and biopsies should be obtained from different sites whenever the diagnosis is unclear, particularly in adults (Nicol & Boguniewicz, 2008). Atopic dermatitis of the hands and feet should be differentiated from tinea or psoriasis. Rarer diseases also should be ruled out, including Netherton's syndrome (in pediatric patients) and cutaneous T-cell lymphoma/mycosis fungoides (in pediatric and adult patients) (see Table 1) (Akdis et al., 2006; Ong & Boguniewicz, 2008).

Table 1.
Differential Diagnosis of Atopic Dermatitis

Dermatologic Diseases
Seborrheic dermatitis Irritant or allergic contact dermatitis Psoriasis Nummular pilaris Keratosis pilaris Lichen simplex chronicus Pityriasis rosea Nonbullous congenital ichthyosiform erythroderma
Neoplastic Diseases
Cutaneous T-cell lymphoma Letterer-Siwe disease Necrolytic migratory erythema associated with pancreatic tumor
Immunodeficiencies
Immune dysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome Hyper IgE syndrome Wiskott-Aldrich syndrome Severe combined immunodeficiency syndrome
Infectious Diseases
Human immunodeficiency virus-associated eczema Scabies Candidiasis Tinea versicolor
Congenital and Metabolic Disorders
Netherton's syndrome Phenylketonuria Zinc deficiency Essential fatty acid deficiency Histidine deficiency Infantile-onset multiple carboxylase deficiency

Source: Adapted with permission from Ong & Boguniewicz, 2008. © Elsevier, Inc.

Skin Barrier Dysfunction In AD

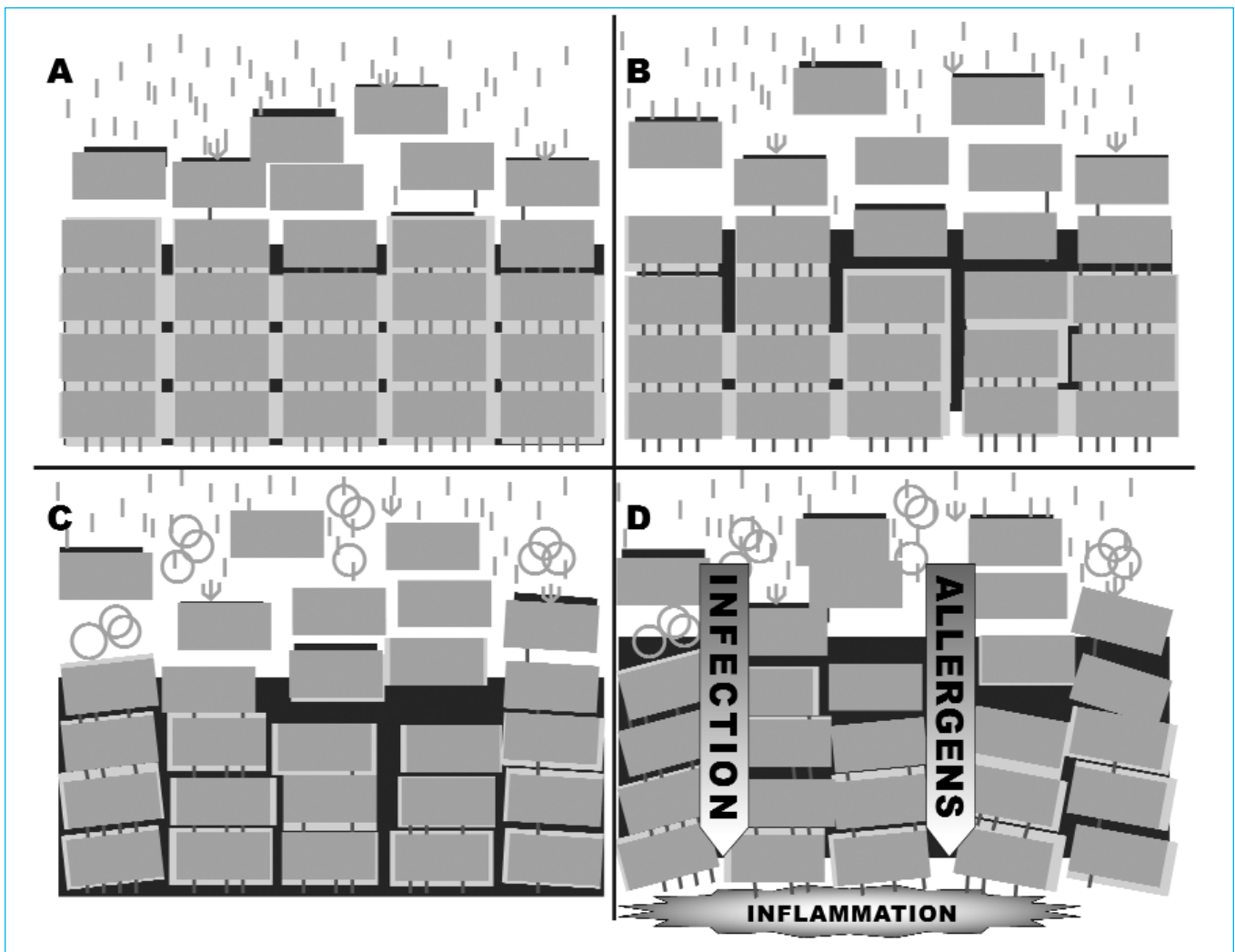
The outermost epidermal layer (stratum corneum) plays a key role in the pathogenesis of AD. The stratum corneum is a dense protein-lipid matrix that prevents epidermal water loss and functions as a barrier to irritants, allergens, and infectious organisms. This barrier undergoes constant renewal, and its thickness is constant (Jensen et al., 2004; Palmer et al., 2006).

In patients with AD, the stratum corneum is susceptible to environmental damage and allergen penetration through the skin (Jakasa, Verberk, Esposito, Box, & Kezic, 2007; Proksch et al., 2006). Hydration is impaired in AD as well; transepidermal water loss, a marker of barrier function, is increased up to fourfold in lesional skin compared with healthy skin (Proksch et al., 2006).

Genetic linkage studies have highlighted the importance of the chromosome 1q21, which contains a collection of genes known as the epidermal differentiation complex. Mutations of the filaggrin gene, located in the epidermal differentiation complex, have been identified as a strong predisposing factor for AD (Howell et al., 2007; Palmer et al., 2006; Weidinger et al., 2008). Such mutations can cause loss or reduction of the filaggrin protein, which is essential for the formation and hydration of the skin barrier. Reduced expression of filaggrin is found in AD, especially in lesional skin (see Figure 1) (Cork et al., 2006; Proksch et al., 2006).

Atopic dermatitis skin is deficient in antimicrobial peptides needed to defend against bacteria, fungi, and viruses (Ong et al., 2002), which may explain increased susceptibility to skin infections. This vulnerability

Figure 1.
Epidermal Skin Barrier Breakdown in Atopic Dermatitis (AD)



(A) In individuals with healthy skin, the stratum corneum is intact. (B/C) In individuals genetically predisposed to AD, breakdown of the stratum corneum is evident. (D) Skin barrier breakdown allows the penetration of environmental agents such as allergens and bacteria.

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highlights the importance of skin care measures aimed at maintaining a healthy skin barrier. Most patients with AD are colonized by *Staphylococcus aureus*. More than half of these patients develop immunoglobulin E molecules directed against toxins known as superantigens produced by *S. aureus* strains (Ong & Leung, 2006). These superantigens dysregulate normal immune responses in patients with AD compared with healthy individuals. Moreover, superantigens are implicated in the induction of corticosteroid insensitivity, which complicates treatment response to corticosteroid therapy in patients with AD (Hauk & Leung, 2001).

Management of AD

Patient education is the foundation of the successful management of AD. However, the typical clinic visit may not provide adequate patient education or optimal patient-provider communication because of time constraints. Studies have demonstrated optimal education provided by a specialist dermatology nurse resulted in an 89% reduction in the severity of AD symptoms (Cork et al., 2003), further reinforcing the critical role of patient-provider communication.

Nurses and NPs should provide both oral and written instructions on the recommended skin care regimen.

Since patients or caregivers may forget or confuse skin care regimens, these details should be reviewed and modified, if necessary, at followup visits. Patients also should understand the chronic and often relapsing nature of AD, so realistic treatment expectations and goals can be established.

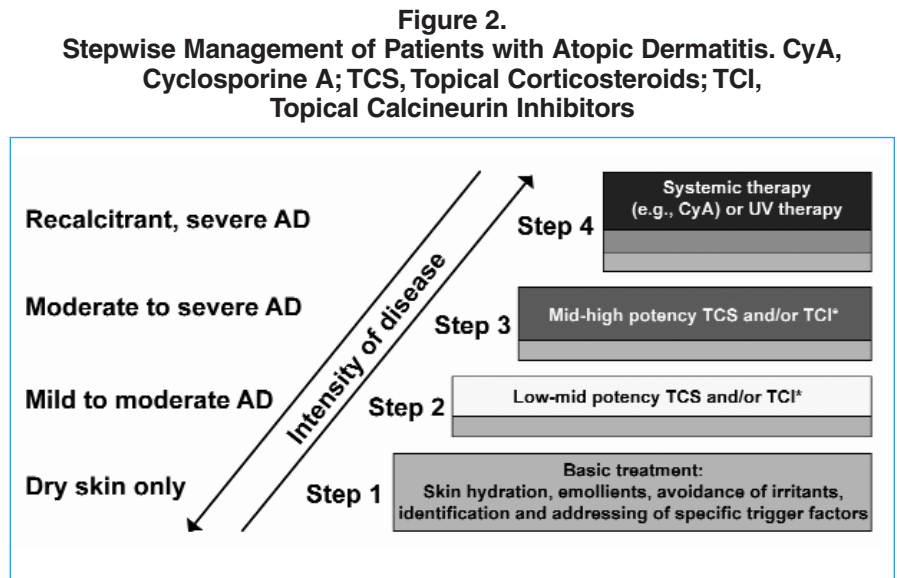
Patients with moderate-to-severe chronic AD symptoms often search for a unique trigger whose avoidance will result in improved control of the disease. A key goal in the successful management of AD is to educate patients about irritants, allergens, and other potential triggers and help them identify circumstances to avoid, reducing the itch-and-scratch

cycle (Leung, Boguniewicz, Howell, Nomura, & Hamid, 2004).

Common irritants include soaps, detergents, toiletries containing alcohol or astringents, solvents, alkalis, and acids. Clothing made from an irritating synthetic or wool material should be avoided in favor of loose-fitting, nonabrasive, and breathable cotton or cotton-blend materials. Hot water during showering or bathing can contribute to skin irritation when flushing occurs, as can excessive sun exposure, especially sunburn. When irritants are identified as triggers, cotton gloves may be used to prevent contact of the irritant with the hands. Cotton gloves also can be used to decrease scratching trauma to the skin and are commercially available in pediatric sizes.

Allergens include dust mites, animal dander, weeds, molds, and pollen. While complete avoidance of such aeroallergens may not be possible, control measures should be taken in patients with a documented sensitization by testing as well as clinical history. Food allergies may exacerbate AD as well, particularly in children less than 3 years of age. Foods that may trigger symptoms in sensitized patients include eggs, milk, wheat, soy, and peanuts. While there are no consensus guidelines on diet for patients with AD, dietary restrictions are recommended in patients with an established diagnosis of food allergy (Akdis et al., 2006). Care must be taken to only restrict specific food allergens that have been implicated in controlled challenges. Extensive elimination diets are rarely required.

In response to the wide variation in the diagnostic and therapeutic management of AD practiced by clinicians, the American Academy of Allergy, Asthma and Immunology and the European Academy of Allergy and Clinical Immunology issued consensus guidelines for clinical practice. These guidelines recommend three basic components of optimal skin care. First and foremost, the regular use of moisturizers or emollients in conjunction with skin hydration is essential to address the skin barrier defect. Second, identification and avoidance of specific and nonspecific triggers is critical in reducing symptoms. Third, depending on the severity of AD, topical therapeutic agents may be initiated in a stepwise fashion. These topical agents include glucocorticosteroids and calcineurin inhibitors.



*Over the age of 2 years.

Source: Reprinted with permission from Akdis et al., 2006. © American Academy of Allergy, Asthma, and Immunology, and the European Academy of Allergy and Clinical Immunology.

Severe refractory disease may be managed with systemic treatments (Akdis et al., 2006) (see Figure 2).

Treatment Strategies

As emphasized in clinical guidelines (Akdis et al., 2006; Eichenfield, 2004), proper daily skin care remains a cornerstone of AD treatment. Patients should receive detailed instructions on washing with appropriate cleansers and moisturizing with appropriate emollients. Cleansers that are mild, fragrance-free, dye-free, and pH-neutral should be used. Patients should be instructed not to scrub with a washcloth and to use warm water. Emollients such as ointments, creams, and lotions should be fragrance-free and contain minimal preservatives; they are most hydrating when used immediately after bathing. The judicious use of moisturizers can increase elasticity of the stratum corneum (Lebwohl & Herrmann, 2005) and improve overall epidermal barrier function (Loden, Andersson, & Lindberg, 1999), thereby making the skin less susceptible to irritants, allergens, and other triggers of flares. By supplying the stratum corneum with lipids to promote skin barrier repair, moisturizers may decrease the need for topical medications, including corticosteroids (Lebwohl & Herrmann,

2005). It is important to emphasize moisturizers should not be applied over or immediately before topical medications; otherwise, they may dilute or prevent penetration of medication into the skin.

Because of reduced epidermal barrier function, patients with AD have a higher risk of recurrent bacterial infections of the skin. Antibiotic treatment may be appropriate for these patients.

Topical Corticosteroids

Topical corticosteroids have been the predominant first-line treatment for moderate-to-severe AD for several decades. They are classified in seven potency groups based on cutaneous vasoconstriction tests, with the most potent in class I and the least potent in class VII. Ointments are more occlusive than creams, gels, lotions, or foams and are associated with a higher degree of systemic absorption compared with the other vehicles (Pariser, 2009). When devising an overall treatment strategy, the choice of which formulation to use depends on the site and severity of the flare as well as patient age and preference. As drug penetration is typically highest in thin skin areas of the body, such as eyelids and genitals (Pariser, 2009), only mild-to-moderately potent preparations of corticosteroids should be

used in these areas. Low-potency topical corticosteroid preparations that contain other active ingredients, such as pramoxine, may also be safe and effective at relieving itch and inflammation in sensitive skin areas.

Adverse effects associated with topical corticosteroids are well documented. The higher the potency of the topical corticosteroid, the greater the risk for adverse effects. Long-term use of moderately potent preparations may cause thinning of the stratum corneum, thereby permitting entry of irritants and allergens that can perpetuate the cycle of irritation and inflammation in AD. Topical corticosteroids also inhibit collagen synthesis and can cause hypopigmentation, skin atrophy, rosacea, acne, and increased hair growth (Draeos, 2008). Systemic adverse effects associated with the long-term use of mid to mid-high potency preparations include adrenal suppression and growth suppression (Pariser, 2009).

To limit the risk of adverse effects, topical corticosteroid preparations should be used only as short-term or intermittent therapy and generally no more than twice daily. Low-potency corticosteroids are associated with fewer adverse effects than are those with higher potency. However, treatment strategy decisions should also balance the need for symptom relief, as insufficient potency also contributes to suboptimal control of AD symptoms.

Topical Calcineurin Inhibitors

Topical calcineurin inhibitors are effective nonsteroidal alternatives in the treatment of AD. Two topical calcineurin inhibitors are available: pimecrolimus cream (1%) and tacrolimus ointment (0.03% and 0.1%). As they do not cause skin atrophy, these nonsteroidal agents may be particularly useful in treating flares on the face, including perioral and periorcular areas (Iskedjian, Piwko, Shear, Langley, & Einarson, 2004; Ong & Boguniewicz, 2008). Topical calcineurin inhibitors are associated with statistically significant improvements in AD patient and parent/caregiver quality of life outcomes (Boguniewicz et al., 2007).

Pimecrolimus is indicated as second-line therapy for the short-term and non-continuous chronic treatment of mild-to-moderate AD in non-immunocompromised adults and children 2 years of age and older who have failed to respond adequately to other

topical prescription treatments, or when those treatments are not advisable (Novartis Pharmaceuticals, 2009). Pimecrolimus demonstrated sustained efficacy in pediatric populations, as indicated by studies of up to 26 weeks (Langley et al., 2008). The use of pimecrolimus at the first signs of new exacerbations appears to prevent progression to major flares and prolongs the time to the first relapse (Gollnick et al., 2008). Pimecrolimus is effective in the long-term management of mild-to-moderate facial flares in children (Zuberbier & Brautigam, 2008) and adults, including eyelid dermatitis (Murrell et al., 2007). In a 12-week study investigating the treatment of facial AD in adults who were intolerant of or dependent on topical corticosteroids, pimecrolimus was associated with a significantly higher percentage of patients who became clear or almost clear of facial lesions compared with vehicle controls (46.5% vs. 16.2%, respectively) (Murrell et al., 2007). Similar efficacy results were obtained in a study of children ages 2-11 years with mild-to-moderate facial AD and dependence on or intolerance of topical corticosteroids, with statistically significant improvements in head and neck symptom severity and time to clearance (Hoeger et al., 2009). Pimecrolimus used at the first signs or symptoms of AD can eliminate or reduce the need for topical corticosteroids. In a 6-month study of adults with AD randomly given pimecrolimus 1% or vehicle cream, in the subgroup of patients with moderate AD, those who received pimecrolimus (n=62) averaged fewer days requiring corticosteroid treatment compared with those receiving vehicle (n=68) (9.5 ± 19.8 days vs. 37.0 ± 36.3 days, respectively) (Meurer et al., 2002). A mild transient burning sensation at the time of pimecrolimus application can occur, similar to the effect of tacrolimus 0.03% (Ellis et al., 2003).

Tacrolimus ointment, both 0.03% and 0.1% for adults and only 0.03% for children aged 2-15 years, is indicated as second-line therapy for the short-term and non-continuous chronic treatment of moderate-to-severe AD in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for AD or when those treatments are not advisable (Astellas Pharma US, Inc., 2009). The anti-inflammatory efficacy of tacrolimus 0.1% is similar to a

potent topical corticosteroid and is greater than mild topical corticosteroids such as hydrocortisone acetate 1% (Ashcroft, Dimmock, Garside, Stein, & Williams, 2005; Yan, Chen, Wang, Zhou, & Wang, 2008). A common adverse effect associated with tacrolimus is a burning or stinging sensation on the site of application, which is significantly greater than with topical corticosteroids (Rustin, 2007). Systemic absorption of tacrolimus appears to be minimal, indicating a lower risk of adverse events compared with corticosteroids (Undre, Moloney, Ahmadi, Stevenson, & Murphy, 2009). Low-dose intermittent, twice-weekly application of 0.1% tacrolimus has shown clinical potency in reducing the number and frequency of flares (Ehrchen, Sunderkötter, Luger, & Steinhoff, 2008).

Several years after the approval of pimecrolimus and tacrolimus, rare cases of lymphoma and skin malignancy have been reported following their use in children and adults. No causal relationship has been demonstrated; nevertheless, this has given rise to theoretical concerns about the safety of topical calcineurin inhibitors in the treatment of AD, which resulted in a black box warning associated with the drug (Astellas Pharma US, Inc., 2009; Fonacier et al., 2005; Novartis Pharmaceuticals, 2009). Several professional medical organizations have published statements asserting the available data show low systemic absorption and no associated increased risk of malignancy or immunosuppression (Fonacier et al., 2005; Ring et al., 2005). Recent studies of large patient populations found no increased risk of lymphoma (Arellano, Wentworth, Arana, Fernandez, & Paul, 2007). Surveillance is ongoing (Spergel & Leung, 2006).

Other Therapies

Although it is beyond the scope of this article to provide a comprehensive account of other therapies, they deserve a brief mention, to expand understanding of the array that may be used to treat AD. Systemic medications such as cyclosporine A may be used for severe, recalcitrant AD, although systemic adverse effects, including renal toxicity, are an enduring concern. Systemic corticosteroids are rarely indicated in the treatment of AD except for short courses while other treatment measures are being instituted. Some patients as well as physicians prefer systemic steroids to

time-consuming skin care with hydration and topical therapy. However, the dramatic clinical improvement that may occur is frequently associated with severe rebound flaring of AD when steroids are discontinued (Nicol & Boguniewicz, 2008).

Wet-wrap therapy can be used on severely affected areas of dermatitis to increase hydration and absorption of topical therapy (Boguniewicz, Nicol, Kelsay, & Leung, 2008; Nicol, 1987). Ultraviolet light therapy can induce temporary remission of symptoms, but the lack of long-term, randomized, controlled data on the use of this treatment limits its clinical utility. Other experimental treatments include methotrexate, mycophenolate mofetil, azathioprine, and intravenous immunoglobulin (Ong, 2009; Ong & Boguniewicz, 2008).

Conclusion

Patient education is paramount in managing AD. The itch-and-scratch cycle of AD exacerbates symptoms, and breaking this cycle is critical in managing this chronic disease. Providing patients with detailed verbal and written instructions about proper daily skin care is key in optimizing clinical outcomes. Improper bathing and moisturizing are common causes of symptom exacerbation. Patients are often confused by the apparent contradiction bathing can both dry and hydrate the skin. Proper soaking and sealing of the skin leads to rehydration, sealing in of moisture, and repair of the damaged epidermal barrier. Even with conscientious skin care, however, patients usually still require pharmacologic treatment.

Treatment should be individualized according to patient characteristics and disease severity. A combination approach may be used to calm the flare with a topical corticosteroid for several days, followed by initiation of a topical calcineurin inhibitor. Topical calcineurin inhibitors are particularly useful in treating the face and other thin, sensitive areas of the skin. Patients should be advised about the potential side effects of selected pharmacologic treatment, as compliance increases when patients know what to expect with treatment. With support and education, patients can learn to anticipate and avoid triggers as well as effectively treat flares when they occur. ■

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