A chronic pruritic skin disorder with a relapsing pattern, atopic dermatitis (AD) affects individuals of all ages, although its prevalence is highest in children. While the pathophysiology of AD is not yet fully understood, genetically-based alterations in barrier function have recently been described, leading to enhanced understanding of the need to maintain the barrier function in this skin disorder. In light of these findings, barrier repair and skin moisturization have emerged as important strategies for patient management, in conjunction with the use of standard therapies for AD. These standard therapies include topical steroids and topical calcineurin inhibitors as well as education to prevent flares and control infection. Proper bathing techniques and avoidance of trigger factors are essential components of an atopic dermatitis treatment regimen.

Although topical therapies can effectively treat most cases of mild-to-moderate atopic dermatitis, patient management is often challenging. Most patients will require the concomitant use of several topical agents; and the regimen will change along with the natural course of the skin disease. More severe patients may require regimens that include phototherapy or systemic medications. Clinicians must be adept at devising effective regimens, educating patients on their proper use, and tailoring long-term care to the patient/caregiver needs.

Take-Home Tips. Barrier repair and skin moisturization have emerged as important strategies for patient management, in conjunction with the use of standard therapies for AD. Standard therapies include topical steroids and topical calcineurin inhibitors as well as education to prevent flares and control infection. Proper bathing techniques and avoidance of trigger factors are essential components of an atopic dermatitis treatment regimen. Most patients will require the concomitant use of several topical agents; and the regimen will change along with the natural course of the skin disease.
Atopic Dermatitis

Presentation and Incidence
Atopic dermatitis is a chronic, inflammatory, relapsing–remitting skin condition that varies in morphology. Features include xerosis, pruritus, and subsequent lichenification from repetitive scratching, with facial erythema and extensor involvement the usual distribution in infants and children. Atopic dermatitis is often associated with a personal or family history of atopy (such as allergic rhinitis, atopic dermatitis, and asthma) and may be associated with immunoglobulin E (IgE) reactivity. Spontaneous remission of atopic dermatitis can occur in children; approximately 60 percent of individuals affected in childhood are clear of disease or symptom-free by early adolescence. Early-onset disease, a family or personal history of atopy, and disease severity may indicate more persistent atopic dermatitis.

Reliable data regarding the incidence of AD in the US population are lacking. Estimates suggest the lifetime prevalence of atopic dermatitis in school-aged children in European countries to be between 10 and 20 percent. With a reported range from over 20 percent to nearly 30 percent, Japan has the highest prevalence of AD. One study suggested that in the Northwest US the prevalence of atopic dermatitis is similar to that in European countries. For reasons that are as yet not understood, the prevalence of atopic dermatitis is higher in developed countries, urban areas, and populations of a higher socioeconomic status. While the incidence of AD in the US is not known with certainty, data reveal that demand for medical care is high. In the seven-year period between 1997 and 2004, pediatric patients (aged 0–18 years) with atopic dermatitis in the US made an estimated 7.4 million office visits for consultation and treatment. As such, treatment may be associated with significant financial costs. Furthermore, atopic dermatitis has an impact on quality of life that involves both the patient and the family. For example, the common complaint of sleep disruption caused by intense pruritus and scratching impedes the affected patient's quality of life and may disrupt the sleep patterns of the entire family.

Etiology
A combination of genetic, immune, neuroendocrine, infectious, metabolic, and environmental factors mediates the development of atopic dermatitis. Current understanding holds that dysfunction of the epidermal barrier is a hallmark of the disease. One area of recent research is the role of filaggrin, a filament aggregating protein, in the pathogenesis of AD. Studies have uncovered loss of function mutations in the gene that encodes filaggrin (FLG) in up to 50 percent of patients with atopic dermatitis. Filaggrin deficiency contributes to faulty epidermal barrier function. Defects in the epidermal barrier of AD patients also result from reduced levels of key lipids (ceramides, cholesterol, and fatty acids), which lead to enhanced transepidermal water loss (TEWL) and decreased moisture content of the stratum.
Corneum. Barrier dysfunction permits increased permeability of hydrophilic substances and increased allergen and microbial absorption.1,3,15

Skin inflammation, a key finding in atopic dermatitis, is mediated by the expression and production of pro-inflammatory cytokines such as interleukin-1 (IL-1), granulocyte-macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor (TNF-α) by keratinocytes in response to mechanical injury or irritation of the skin.16 Additional inflammatory cells, including monocytes, T cells, and eosinophils, are recruited into the skin. In acute atopic dermatitis, the production of the T-helper type 2 (TH-2) immune response predominates with the production of IL-13 and IL-4 and the activation of IgE synthesis.3

Topical Treatment
Treatment of AD is aimed at managing symptoms with the ultimate goal of inducing remission and reducing the frequency and severity of flares.1,2 As such, the approach to each patient must be individualized to the specific presentation and must be modified over the long-term to meet the patient’s needs.

Skin care and barrier repair devices. Proper skin care is essential for management of atopic dermatitis. Patients should bathe with mild, soap-free cleansers that are free of fragrances and detergents (bubble baths).17 Standard emollients can be applied to improve skin hydration and reduce dryness and flaking. Applying emollients immediately after bathing and patting the skin dry maximizes absorption and increases skin hydration.

New barrier repair devices have come to market. These are designed specifically to address the underlying defects in the epidermal barrier of patients with AD. Prescription barrier repair devices include MimyX (Stiefel/GlaxoSmithKline), Atopiclair (Graceway Pharmaceuticals), EpiCeram (Promius Pharma), and Hylatopic (Onset Therapeutics),18 all of which contain ceramides, cholesterol, and fatty acids along with proprietary ingredients intended to increase hydration and reduce inflammation. Over-the-counter products formulated with ceramides and intended to support barrier function include CeraVe (Coria Laboratories) and the Aveeno Advanced Care line of products.

By replacing these key lipids, which are reduced in atopic dermatitis, these topical agents repair barrier function, reduce trans-epidermal water loss, and increase the moisture content of the skin. These non-steroidal emulsions effectively relieve symptoms associated with AD, including pruritus, burning, and xerosis and can reduce the need for topical corticosteroid use.18-20 Application of these agents is safe for all parts of the body including the face, without the adverse effects associated with the use of topical corticosteroids and calcineurin inhibitors.

Atopiclair is reported to be effective as a monotherapy in treating mild-to-moderate atopic dermatitis in infants and children.21,22 In a randomized trial of 113 subjects, EpiCeram was reported to be equally effective as fluticasone propionate 0.05% for treating atopic dermatitis.23

Topical corticosteroids. Topical corticosteroids,
which have been the mainstay of atopic dermatitis therapy for more than 40 years, are still considered first-line therapy for acute flares. Most patients with atopic dermatitis will be managed with a topical corticosteroid at some point during the course of treatment. However, corticosteroids are not ideal for long-term management of AD. With immunosuppressive, anti-inflammatory, vasoconstrictive, and antiproliferative properties, topical corticosteroids suppress the release of pro-inflammatory cytokines and reduce the activity of various immune cells, including T lymphocytes, monocytes, and macrophages.

Despite their therapeutic utility, topical corticosteroids are associated with potential local and systemic adverse effects, the incidence of which increase with the potency of corticosteroid used and the duration of therapy. When applied to areas of thin skin, such as the face, groin, neck, and axillae, topical corticosteroids may have greater potency than when applied to other anatomic locations, and local adverse effects tend to occur more frequently in these areas. Potential local adverse effects of topical corticosteroid use include skin atrophy, striae, prominent telangiectasias, perioral dermatitis, acne, increased spread of fungal infections, hypopigmentation, rosacea, cataracts, and glaucoma. When topical corticosteroids are prescribed and used properly, complications associated with use rarely develop. However, potential systemic adverse effects such as reduction of the linear growth rate in children and reduced bone density have been reported.

Selection of a topical corticosteroid is based upon the potency (from low to super-potent) and vehicle type. Due to the fact that the risk of adverse events increases with the potency of the corticosteroid, the site of application, and the duration of use, the clinician must weigh these considerations when selecting an agent. A general approach is to treat an acute flare of atopic dermatitis with up to two to four weeks of medium-to-high-potency topical corticosteroid ointments applied to the affected areas of spongiotic dermatitis to induce partial remission. Once partial remission is attained, the clinician may taper down the frequency to as little as twice-weekly application of a less-potent preparation to maintain long-term control of disease activity. When topical corticosteroids are used for maintenance therapy, the least potent, effective formulation should be selected.

Some parents and even clinicians eschew the use of higher potency corticosteroids, citing concerns about side effect risks. However, using higher potency corticosteroids in appropriate settings may actually reduce the patient’s exposure to the corticosteroid, and thereby possibly reduce the risk of adverse events. A randomized, controlled trial in children with mild-to-moderate atopic dermatitis revealed that shorter periods of potent topical corticosteroid use were as effective as prolonged use of a low-potency preparation in controlling flares. Reducing the number of daily applications may be an appropriate method to decrease overall corticosteroid exposure. Interestingly, one large systematic review found that using twice-daily application of topical corticosteroid was no more effective than once-daily application. From a clinical standpoint, it may be worthwhile to explain to caregivers that the concentration of a topical corticosteroid formulation (i.e., the number behind the brand name) does not indicate its potency. For example, hydrocortisone butyrate 1.0% lipocream is a class V, lower-mid-strength corticosteroid, while clobetasol propionate 0.05% foam is a class I, superpotent formulation.

Although uncommon, reversible suppression of the hypothalamic–pituitary–adrenal (HPA) axis can occur with frequent and chronic use of topical steroids. This systemic side effect seems to be associated with increased percutaneous absorption caused by a higher ratio of skin surface area to body mass in children. Systemic absorption occurs more often in children with severe disease, possibly due to the disrupted barrier and subsequently increased absorption of drug. Long-term topical corticosteroid use is generally not recommended. If this therapeutic approach is mandated by the patient’s overall status, care should progress under careful physician supervision and may require dietary intervention (such as adequate calcium and vitamin D intake) to help offset systemic side effects.
Given the known risks associated with prolonged use of topical corticosteroids, controlled studies of extended durations of use are limited. However, data support the safety of specific formulations for continuous use beyond two weeks. Application of fluticasone propionate cream and lotion 0.05% (Cutivate Cream and Lotion, PharmaDerm), desonide hydrogel and foam 0.05% (Desonate hydrogel, Intendis; Verdeso foam, Stiefel/GlaxoSmithKline), or hydrocortisone butyrate 0.1% (Locoid Lipocream, Triax) for up to four weeks has been found to be safe in children as young as three months.

The choice of vehicle—whether cream, ointment, gel, hydrogel, foam, or oil—can influence the potency of an agent, influence tolerability, and may have implications for patient adherence. Ointments are generally more potent than creams. Patients may prefer certain vehicle bases (such as a foam for quick application to large surface areas) and refuse others (such as ointments for the face or axillae). Importantly, the vehicle base of corticosteroid creams may contain preservatives that can cause an irritant contact dermatitis, though these are rare. Ointments usually contain fewer sensitizing ingredients than lotions or creams. Some vehicle bases are formulated with peanut oil or peanut oil derivatives; several studies show that patients with a known peanut allergy can safely use specific topical preparations containing peanut oil without developing a local or systemic reaction.

Wet wrap therapy in conjunction with topical corticosteroids (see sidebar) is gaining popularity in AD management.

**Topical calcineurin inhibitors.** Now used for nearly a decade, topical calcineurin inhibitors (TCIs) tacrolimus and pimecrolimus are FDA-approved for use as second-line therapy in treating atopic dermatitis in immunocompetent patients over the age of two years. The product labeling indicates that these agents are to be used for short-term and non-continuous chronic treatment in children ages two years of age and older who have failed to respond to other topical pharmacological treatments.

Tacrolimus ointment 0.03% (Protopic, Astellas, approved for children ages two to 15 years) and 0.1% is approved to treat moderate-to-severe atopic dermatitis, whereas pimecrolimus cream 1% (Elidel, Novartis) is approved to treat mild-to-moderate atopic dermatitis. Both tacrolimus and pimecrolimus decrease skin inflammation by inhibiting T-cell activation and the transcription and release of inflammatory cytokines.

Clinically, TCIs are thought of as steroid-sparing agents. As such, they are typically used for maintenance therapy as an alternative to topical corticosteroids and are advantageous in sensitive skin areas, such as the head and neck, that are more prone to adverse effects associated with the use of topical corticosteroids. A common therapeutic approach is to initiate therapy with TCIs at the same time that a topical corticosteroid is introduced. The corticosteroid provides a more rapid onset of action, but when it is tapered or withdrawn at two weeks the TCI should be demonstrating efficacy.

Multiple studies have shown that twice-daily application of topical pimecrolimus cream 1% for three to six weeks and even up to two years is well tolerated, effectively controlled atopic dermatitis disease activity, reduced the number and severity of flares, and reduced the need for topical corticosteroid treatment. Long-term studies of topical tacrolimus show rapid efficacy and safety for the management of atopic dermatitis in children and adults for up to four years. Results of a four-year, long-term study showed that the adverse events profile was similar to that reported in previous one-year studies; no new adverse events were reported.

Reviews that compare topical tacrolimus to topical pimecrolimus found no significant difference in the overall safety or efficacy between tacrolimus ointment 0.03% and pimecrolimus cream 0.1%. A review of three randomized, controlled trials comparing tacrolimus to pimecrolimus found that tacrolimus was more effective and had a more rapid onset of action than pimecrolimus in treating adults and children with moderate-to-severe atopic dermatitis. There were no significant differences in the incidence of adverse events between the therapies.

Data and clinical experience suggest that topical tacrolimus application may be associated with a
higher incidence of application site reactions—which include erythema, irritation, burning, and pruritus—and that these reactions persist for a longer amount of time.\textsuperscript{43,47,54,55} When TCI therapy is implemented in conjunction with a topical corticosteroid, the latter may minimize the development of application site reactions.

Some concerns about lymphoproliferative disease, immunosuppression, and nonmelanoma skin cancer associated with the use of topical application of tacrolimus and pimecrolimus have been raised. Studies show that there is some percutaneous absorption associated with topical application of these agents, however the amount is not significant to cause immunosuppression comparable to that experienced by immunodeficient patients or transplant patients who require systemic immunosuppressants to prevent organ rejection.\textsuperscript{43,47} Topical pimecrolimus has been found to have less percutaneous absorption than both topical tacrolimus and topical corticosteroids, perhaps due to its lipophilicity and higher molecular weight.\textsuperscript{56} Initial studies of patients with exposure to topical calcineurin inhibitors show no association with an increased risk of nonmelanoma skin cancer.\textsuperscript{57}

### Oral Agents

**Antihistamines.** Small studies and anecdotal reports have suggested that the use of either sedating or non-sedating oral antihistamines, which are known to be safe for use in children, can relieve the pruritus associated with atopic dermatitis, however, the available data are limited by small sample sizes or sub-optimal trial design.\textsuperscript{56} Sedating antihistamines may be given at bedtime to promote sleep despite pruritus.\textsuperscript{56} First generation, sedating antihistamines, such as diphenhydramine and hydroxyzine, can increase the total sleep time and decrease nocturnal awakenings—common sleep disturbances associated with scratching episodes in patients with atopic dermatitis.\textsuperscript{56-61} These agents should be administered at bedtime. There is less evidence that the more expensive, second-generation antihistamines reduce pruritus associated with atopic dermatitis, although one study found that twice-daily fexofenadine used

### Treatment Principles Summary

<table>
<thead>
<tr>
<th>Agent</th>
<th>Acute Flare</th>
<th>How Used</th>
<th>Recurring Flare</th>
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<tbody>
<tr>
<td><strong>Basic Skincare</strong></td>
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<tr>
<td>Gentle, soap-free, fragrance-free cleansers for bathing. After bathing, pat the skin dry and immediately apply fragrance-free emollients (creams and ointments preferred) to “lock-in” moisture and optimize hydration.</td>
<td>Always</td>
<td>Always</td>
<td>Always</td>
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<tr>
<td><strong>Barrier Repair</strong></td>
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<tr>
<td>Regular application of barrier repair cream/device to enhance barrier repair and proper epidermal barrier function.</td>
<td>Often/Always</td>
<td>Often/Always</td>
<td>Often/Always</td>
</tr>
<tr>
<td><strong>Topical Corticosteroids (CS)</strong></td>
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<tr>
<td>High-potency for control of acute flares, applied once-daily for about two to four weeks.</td>
<td>Often as monotherapy or + TCI</td>
<td>Not recommended</td>
<td>Sometimes; +/- TCI</td>
</tr>
<tr>
<td>Low-potency for acute flares of mild AD, applied once-daily for up to four weeks (depending on formulation) and for new on-set flares.</td>
<td>Sometimes as monotherapy or + TCI</td>
<td>Sometimes, for short durations only</td>
<td>Sometimes; +/- TCI</td>
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<tr>
<td><strong>Topical Calcineurin Inhibitors (TCI)</strong></td>
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<tr>
<td>May be initiated with topical corticosteroids because they have a slower onset of action than CS; should be used twice daily.</td>
<td>Often + CS; Rarely as monotherapy</td>
<td>Often as monotherapy</td>
<td>Sometimes; Often +CS</td>
</tr>
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</table>
in conjunction with topical corticosteroids was effective in reducing pruritus in patients with AD. Second generation antihistamines may also help reduce any concurrent symptoms of chronic urticaria or allergic rhinitis.

**Antibiotics.** A significant proportion (up to 90 percent) of adults and children with atopic dermatitis are colonized with *Staphylococcus aureus* in both clinically affected and unaffected skin and the anterior nares. Features of atopic skin, such as a more alkaline pH, a defective epidermal barrier function, and decreased production of antimicrobial peptides, encourage bacteria to adhere to the skin and flourish. The presence of *S. aureus* can contribute to inflammation by encouraging the production of superantigens, which activate the production and release of pro-inflammatory cytokines from keratinocytes.

Oral antibiotics can significantly reduce bacterial colonization and are shown to reduce atopic dermatitis severity in patients with clinical evidence of secondary bacterial infections. However, evidence does not support the use of oral antibiotics in pediatric AD patients with no evidence of secondary bacterial infection. There are concerns about the development of bacterial resistance associated with long-term oral and topical antibiotic use, and cessation of therapy may be associated with re-colonization. Therefore, long-term use of topical or oral antibiotics for the management of atopic dermatitis should be avoided.

Sodium hypochlorite (bleach) baths and application of nasal mupirocin represent low-cost alternatives to reduce the severity of atopic dermatitis in children. Adjunct treatment with bleach baths may help decrease the number of skin infections and the need for oral antibiotics.

**Overcoming Challenges**

Despite advancements in understanding the pathogenesis of AD, including genetic factors and the role of barrier dysfunction, treatment often remains challenging. Standard and emerging therapies can provide notable improvement in symptoms and improve outcomes. Key to success is devising a management strategy that meets the patient’s and caregivers’ needs while optimizing adherence. Studies confirm the importance of a well-developed patient-provider relationship, which is associated with clinical improvement of atopic dermatitis and decreased use of topical corticosteroids and calcineurin inhibitors.

One important area of dialogue is the relapsing-remitting course of atopic dermatitis. Patients and families must recognize this reality in order to develop appropriate short- and long-term treatment expectations. Although spontaneous remission may occur, there is no “cure” for AD.

To enhance therapeutic outcomes, clinicians must educate patients/caregivers effectively about the proper use of topical corticosteroids, TCIs, and emollients. This includes providing specific information about the amount of medication to apply, the frequency of application, and the order of application. The “finger-tip unit” or FTU may be a useful method for defining the amount of a specific formulation to be applied to the skin. The FTU is the amount of a topical formulation expressed from a tube from the distal skin-crease to the tip of the index finger.

Written instructions or written action plans (WAP) have been shown to improve adherence and treatment outcomes in patients with asthma and appear to provide benefit in the management of AD. It seems likely that written action plans can reduce therapeutic errors (improper application, use of too little or too much medication, even pharmacy prescription filling errors) at home and may reduce the need for calls to the clinic. Proper education of caregivers and patients and good compliance with a regimen that control flares and allows maintenance strategies is essential to a favorable outcome.

Topical therapies traditionally used for atopic dermatitis are safe and effective when used appropriately. Clinicians should devise topical regimens that optimize response in the acute phase, maintain symptom control during the remission phase, and provide quick control of flares. The use of high potency topical corticosteroids for short durations may reduce the patient’s total corticosteroid exposure. Long-term regimens should be aimed at using...
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the least potent effective formulation(s) for the short- est duration of time.


70. Mettry D, Brownin J, Rousseau et al. Sodium hypochlorite (bleach) baths: a potential measure to reduce the incidence of recurrent, cutaneous Staphylococcus aureus superinfection among susceptible populations. Poster presented at the Society for Pediatric Dermatology annual meeting; July 12–15, 2007; Chicago, IL.