A Review of Treatment of Mild to Moderate Pediatric Atopic Dermatitis

A specialist shares insights on the management of patients with atopic dermatitis with an emphasis on topical interventions and long-term management strategies.

By Adelaide A. Hebert, MD

Treatment of AD is aimed at managing symptoms with the ultimate goal of inducing remission and reducing the frequency and severity of flares. 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). 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 Plus (Onset Therapeutics), some 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), the Aveeno Eczema Care line of products (Johnson & Johnson Consumer Health), and Cetaphil Restoraderm (Galderma).

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 emollients effectively relieve symptoms associated with AD, including pruritus, burning, and xerosis and can reduce the need for topical corticosteroid use. 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.

Atopiclair is reported to be effective as a monotherapy in treating mild-to-moderate atopic dermatitis in infants and children. In a randomized trial of 113 subjects, EpiCeram was reported to be...

Take-Home Tips. Standard and emerging therapies can provide notable improvement in symptoms of mild to moderate atopic dermatitis and improve outcomes. Key to success is devising a management strategy that meets the patient’s and caregivers’ needs while optimizing adherence. To enhance therapeutic outcomes, clinicians must educate patients/caregivers effectively about the proper use of skin care, barrier repair formulations, topical corticosteroids, TCIs, and emollients. Written instructions or written action plans (WAP) appear to provide benefit in the management of AD.
equally effective as fluticasone propionate 0.05% for treating atopic dermatitis.9

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.10 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,11 topical corticosteroids suppress the release of pro-inflammatory cytokines and reduce the activity of various immune cells, including T lymphocytes, monocytes, and macrophages.12

Despite their therapeutic utility, topical corticosteroids are associated with potential local and systemic adverse effects, the incidence of which increases 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.1 Potential local adverse effects of topical corticosteroid use include skin atrophy, striae, prominent telangiectasias, perioral dermatitis, acne, worsening 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 with chronic use of topical steroid preparations.13,14

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 spon-

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| 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.1-4 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.4,5 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.1-5

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.6,7 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. Adjuvant treatment with bleach baths may help decrease the number of skin infections and the need for oral antibiotics.6-10

References
8. Metry D, Browning I, 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.
gotic 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.\(^1,3,15\) When topical corticosteroids are used for maintenance therapy, the least potent, effective formulation should be selected.\(^1\)

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 are 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.\(^10\)

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),\(^17,18\) desonide hydrogel and foam 0.05% (Desonate hydrogel, Intendis\(^19\) Verdeso foam, Stiefel/GlaxoSmithKline\(^20\)), and hydrocortisone butyrate 0.1% (Locoid Lipocream, Triax)\(^21\) for up to four weeks has been found to be safe in children as young as three months.

Wet wrap therapy in conjunction with topical corticosteroids (See p. 45 in this edition) 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.\(^22,23\)

Tacrolimus ointment 0.03% (approved for children ages two to 15 years) and 0.1% are approved to treat moderate-to-severe atopic dermatitis, whereas pimecrolimus cream 1% 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.\(^24\)

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.\(^25\) A common therapeutic approach is to initiate therapy with TCIs at the same time that a topical corticosteroid is introduced.

Multiple studies have shown that twice-daily application of topical pimecrolimus cream 1% for three to six weeks and even up to two years was well tolerated, effectively controlled atopic dermatitis disease activity, reduced the number and severity of flares, and reduced the need for topical corticosteroid treatment.\(^26-28\) 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.24,29-35

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%.35 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.34 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.24,28,35,36 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.24,35 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.37 Initial studies of patients with exposure to topical calcineurin inhibitors show no association with an increased risk of nonmelanoma skin cancer.38

**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 out-
comes. 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.30

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. 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.40 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.

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