

# Management of Atopic Dermatitis in the Pediatric Population

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## ABSTRACT

Atopic dermatitis, one of the most common skin disorders in young children, has a prevalence of 10% to 20% in the first decade of life. It is a chronic illness that requires a multifaceted treatment strategy in the setting of limited therapeutic options. Balancing safety concerns with efficacious treatment is of particular importance in the pediatric population. Parents of patients with atopic dermatitis turn to their primary caregivers for guidance regarding this physically demanding and psychologically stressful condition. In addition to serving as a review of atopic dermatitis, this article delves into the state-of-the-art therapeutic options and includes a detailed review of the differences between topical corticosteroids and topical calcineurin inhibitors. We also discuss new treatment strategies that are being used by atopic dermatitis specialists, such as comprehensive "education-as-intervention" models, wet wraps, bleach baths, and systemic immunomodulatory therapies. *Pediatrics* 2008; 122:812–824

## EPIDEMIOLOGY

Atopic dermatitis (AD), well known among pediatricians as a chronic, highly pruritic, inflammatory skin disease, is one of the most common skin disorders in children.<sup>1–3</sup> In developed countries, 10% to 20% of children and 1% to 3% of adults are estimated to be affected.<sup>4</sup> Between 1997 and 2004, pediatric patients with AD (newborn to 18 years of age) accounted for an estimated 7.4 million office visits in the United States alone.<sup>5</sup> Disease onset typically occurs by 1 year of age in ~60% of affected infants and by 5 years of age in ~85% of affected children.<sup>2</sup>

## ETIOLOGY

The clinical manifestations of AD are thought to result from a complex interplay of genetic, immune, metabolic, infectious, neuroendocrine, and environmental factors.<sup>6</sup> Defects in the epidermal barrier function and cutaneous inflammation are 2 hallmarks of AD. Defective epidermal barrier function is thought to be related to the downregulation of cornified envelope genes such as the filament-aggregating protein, filaggrin, reduced ceramide levels, increased levels of endogenous proteolytic enzymes, and enhanced trans-epidermal water loss.<sup>7,8</sup> Barrier function can be damaged further by a lack of certain endogenous protease inhibitors in atopic skin, exogenous proteases from *Staphylococcus aureus* and house dust mites, and the use of soaps and detergents that can raise the local pH and increase activity of endogenous proteases such as stratum corneum chymotryptic enzyme.<sup>9,10</sup> The diminished epidermal barrier function seen in patients with AD likely contributes to increased allergen absorption into the skin and microbial colonization.<sup>11</sup>

Atopic skin inflammation is mediated, at least in part, by a complex, temporal-spatial expression of cytokines and chemokines. Mechanical injury, from trauma, infection, or even simply the scratching of the itch associated with atopic skin, stimulates the local production of primary proinflammatory cytokines such as interleukin 1 (IL-1) and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ). These cytokines bind to vascular endothelium receptors, activate cellular signaling pathways, induce vascular endothelial cell adhesion molecules, and lead to extravasation of inflammatory cells into the skin.<sup>12</sup> Expression of cytokines seems to differ for acute versus chronic AD. Acute AD is associated with the production of T-helper type 2 (Th2) cytokines such as IL-4 and IL-13, which mediate immunoglobulin isotype switching to immunoglobulin E (IgE) synthesis and upregulate expression of adhesion molecules on endothelial cells. Acute AD lesions also contain increased levels of IL-17, a cytokine that induces the release of proinflammatory mediators from macrophages and fibroblasts.<sup>13</sup> In contrast, chronic AD lesions are associated with IL-5, which is involved in eosinophil development and survival, production of the Th1-like cytokines IL-12 and IL-18, and several remodeling-associated cytokines such as IL-11 and transforming growth factor  $\beta$ 1.<sup>11,13</sup> Ongoing research into the roles

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### Key Words

topical calcineurin inhibitors, atopic dermatitis, atopy, management strategies, topical steroids

### Abbreviations

AD—atopic dermatitis  
IL—interleukin  
TNF- $\alpha$ —tumor necrosis factor  $\alpha$   
Th—T helper  
IgE—immunoglobulin E  
FDA—Food and Drug Administration  
TCI—topical calcineurin inhibitor  
FTU—fingertip unit

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**TABLE 1 Diagnostic Considerations for Pediatric AD**<sup>6,14,15,90</sup>

Essential features (must be present)
Pruritus
Eczematous dermatitis (acute, subacute, or chronic)
Typical morphology and age-specific patterns
Chronic or relapsing history
Important features (observed in most cases and providing support to diagnosis)
Early age of onset
Atopy
Personal or family history
IgE reactivity
Xerosis
Associated features (suggest the diagnosis of AD but are too nonspecific to be used as defining/detection criteria for research and epidemiologic studies)
Atypical vascular responses (eg, facial pallor, white dermatographism, delayed blanch response)
Keratosis pilaris/hyperlinear palms/ichthyosis
Ocular/periorbital changes
Other regional findings (ie, perioral changes/periauricular lesions)
Perifollicular accentuation/lichenification/prurigo lesions
Conditions to be excluded
Contact dermatitis (allergic and irritant)
Seborrheic dermatitis
Scabies
Psoriasis
Impetigo
Drug eruptions
Perioral dermatitis
Ichthyoses and keratinization disorders (eg, Netherton syndrome)
Cutaneous lymphoma
Immune deficiency syndromes (eg, Wiskott-Aldrich syndrome, hyper-IgE syndrome, etc)
Zinc deficiency (acrodermatitis enteropathica)
Potential variants/associated characteristics of AD
Ichthyosis vulgaris
Keratosis pilaris
Nummular eczema
Pityriasis alba

of cytokines and the complex immunology of AD may provide additional insight into the development and, ultimately, treatment of this disease.

### DIAGNOSING AD

Diagnosis is based on the presence of a combination of (1) essential, (2) important, and (3) associated clinical features (Table 1) and can present challenges because of the broad differential diagnosis.<sup>14,15</sup> Therefore, when diagnosing AD, physicians must be careful to exclude the possibility of other skin conditions (Table 1).<sup>6</sup> Once the diagnosis has been established, we recommend frequent reevaluation during the clinical course to ensure the accuracy of the diagnosis, to forestall morbidities such as superinfection, to reinforce key management points with parents and patients, and to evaluate and adjust treatment according to clinical response and tolerability. These measures are particularly important for very young patients.

### SIGNIFICANCE OF EARLY AND EFFECTIVE MANAGEMENT

It is important that clinicians recognize AD as a direct threat to an individual child's overall physical and social

well-being and as a disease that affects the family dynamic.<sup>3,16</sup> Pruritus, one of the most common symptoms of AD, often leads to an "itch-scratch" cycle that can compromise the epidermal barrier, resulting in increasing water loss, xerosis, microbial colonization, and secondary infection. The physical changes of AD can affect pediatric patients in a variety of ways including lack of sleep, poor school performance marked by an inability to focus, behavioral problems, low self-esteem, being teased by other children, decreased participation in sports and other social activities, stress, and anxiety. In children with AD, health-related quality-of-life impairment may at least equal that experienced with many other chronic diseases of childhood, including diabetes and cystic fibrosis.<sup>17,18</sup> Families, too, may suffer significant physical, emotional, and functional effects and must be prepared to cope with lifestyle limitations imposed by AD.<sup>19</sup>

From a public health perspective, the prevalence of AD in children has increased steadily over the past several decades and is paralleled by increases in the prevalence of asthma, allergic rhinoconjunctivitis, and the emerging entities of eosinophilic esophagitis and gastroenteritis.<sup>20,21</sup> The epidemiologic linkage among AD, asthma, and allergic rhinitis (also known as the atopic triad) is particularly evident when evaluated in the context of increasing disease severity.<sup>22</sup> The observation that AD is frequently the first disorder of the atopic triad to manifest has led to the concept of the "atopic march," the notion that infants with AD, through epicutaneous sensitization that leads to systemic allergic responses and airway sensitization, are predisposed to developing asthma and/or allergic rhinitis later in childhood.<sup>3,23-25</sup> At least 1 long-term prospective study is investigating the notion that if AD arises early in life, then perhaps prompt recognition and intervention may improve outcomes with respect to the clinical course of AD and influence the subsequent development of asthma and allergic rhinitis.<sup>26</sup> Alternatively, it has also been suggested that these atopic disorders may be independent coexpressions of a common phenotype.<sup>22</sup>

### APPROACHES TO AD MANAGEMENT

Successful management involves educating patients and their families about AD, reducing signs and symptoms of the condition, preventing and decreasing the degree and frequency of flares, modifying the overall disease course, and, possibly, slowing the atopic march.<sup>27</sup> A comprehensive long-term strategy that encompasses education, trigger avoidance, excellent skin care, and treatment (pharmacologic and nonpharmacologic measures) is vital.

Physicians should use their understanding of the variety of available treatment options to develop a personalized therapeutic strategy that is tailored to the individual child's age and needs, extent and localization of AD at presentation, and overall disease course (including persistence, frequent flares, etc). To maximize compliance with treatment recommendations, it is important that physicians be sensitive to parental anxiety about the disease and any real or perceived potential adverse effects of available treatments. For this reason, efficacy and

safety profiles, indications, contraindications, and limitations are important considerations for evaluating pharmacologic treatments.<sup>14</sup> Effective management is also based on close monitoring for changes in disease status (eg, flares) and should entail stepwise treatment that is adjusted in tune with the clinical course to allow for transition from acute flare treatment to chronic maintenance therapy. Guiding the patient and his or her family along a sliding scale of treatment options may enable them to respond appropriately and promptly to minor disease variations and may proactively promote compliance with prescribed therapy. Careful review of in-hand medications (ie, the patient brings all current therapies to the office visit for evaluation of quality/quantity of use) and diligent monitoring of refills are also recommended to assess compliance and potential medication overuse.

### Education as Intervention

Education is emerging as its own primary intervention and is critical in terms of creating realistic expectations based on the knowledge that AD is a complex, chronic disorder. A multicenter, randomized, controlled trial compared children with AD whose parents had received 6 weeks of intensive AD education to those children whose parents did not. The investigators taught age-appropriate interventions to the parents of patients with AD at 7 hospitals in Germany. Educational classes were organized according to age group, with separate once-per-week sessions for the parents of children aged 3 months to 7 years, 8 to 12 years, and 13 to 18 years. Compared with the children of parents who did not receive any extra instruction, patients in all 3 treatment groups demonstrated improved subjective quality-of-life scores and objective measures of eczema severity over the 12-month period.<sup>28</sup>

Paralleling strategies shown to be effective in managing patients with asthma, new models of education are emerging as an essential component of long-term AD management.<sup>29–31</sup> Comprehensive “centers” combine several specialty services (dermatology, allergy, infectious disease, behavioral psychology, etc) with intensive education as a direct intervention for improved care. With longer patient appointments, focused educational curriculums, patient support networks, and the ability to elicit patient feedback, the interventional education model may allow physicians to better impress on caregivers that living with AD should be equated to running a marathon rather than a sprint. Comparative evaluation is required to examine the cost-effectiveness and suitability of these educational programs.<sup>32</sup>

When access to specialized eczema educational facilities is impractical or unnecessary, primary care physicians assume responsibility for educating patients and their families about AD. Topics ranging from trigger avoidance to proper skin care should be addressed, and an explanation that AD has distinct phases that require different types of therapies during each phase should be made. In addition, flares, which may occur despite the best of efforts, should be identified as short-term setbacks that can be overcome. Numerous resources exist on the Internet to assist health care providers in educating

**TABLE 2 Online Resources for Patients With AD and Their Families**

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Coping strategies and support groups
National Eczema Association ( <a href="http://www.nationaleczema.org">www.nationaleczema.org</a> )
Under My Skin: A Kid's Guide to Atopic Dermatitis ( <a href="http://www.undermyskin.com">www.undermyskin.com</a> )
Images of Isolation ( <a href="http://www.nationaleczema.org/Images-Of-Isolation/default.asp">www.nationaleczema.org/Images-Of-Isolation/default.asp</a> )
Specialized AD care
The Eczema Center ( <a href="http://www.eczemacenter.org">www.eczemacenter.org</a> )
National Jewish Medical and Research Center ( <a href="http://www.njc.org">www.njc.org</a> )
EczemaNet ( <a href="http://www.skincarephysicians.com/eczemanet/index.html">www.skincarephysicians.com/eczemanet/index.html</a> )
Information on allergic triggers
American Academy of Allergy, Asthma & Immunology ( <a href="http://www.aaaai.org">www.aaaai.org</a> )
Food Allergy & Anaphylaxis Network ( <a href="http://www.foodallergy.org">www.foodallergy.org</a> )

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and supporting patients with AD and their families (Table 2).

### Avoidance of Triggers

Triggers vary among patients and should be avoided when possible (Table 3). The role of aeroallergens, such as dust mites and animal dander, remains unclear. Although total avoidance of environmental aeroallergens is impossible, measures can be taken to reduce exposure to these factors for patients in whom aeroallergens are suspected of playing a causative role.<sup>33</sup> Mattress covers, low-pile carpet (particularly in sleeping areas), and non-dander-producing pets may be beneficial, particularly for children who have concomitant asthma and/or rhinitis.<sup>34</sup> Food allergens may also serve as triggers for some patients, but parents should be cautioned against extreme restriction diets, which may not only be unhelpful but also can lead to serious malnutrition.<sup>35</sup> It should be emphasized that eliminating specific triggers may not result in clearance of AD; however, avoidance of known triggers is a reasonable approach.

### Breastfeeding

The impact of breastfeeding on the prevention of AD remains under debate.<sup>36–38</sup> Reasons for this controversy include methodologic differences (eg, differences in cri-

**TABLE 3 Potential AD Triggers<sup>1,8,33,34,90</sup>**

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Associated with direct contact
Toiletries containing alcohol, astringents, or fragrances
Harsh detergents/soaps
Abrasive clothing (wool or synthetics)
Associated with physiologic/emotional stressors
Infections (especially from <i>S aureus</i> , viruses, fungi, etc)
Overheating/sweating
Psychological stress
Associated with food
Food allergens found in
Cow's milk
Eggs
Peanuts
Tree nuts (eg, walnuts, cashews)
Soy
Wheat
Fish
Shellfish
Foods processed with any of the above

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**TABLE 4** Different Treatments for Features of AD<sup>1,3,6,16,34,90</sup>

AD Feature	Treatment Option	Mechanism of Action
Xerosis	Emollients, moisturizers, and barrier devices	Moisturize dry skin and help repair the defective skin barrier
Immune dysfunction	Avoidance of triggers	Helps prevent known allergic reactions and inflammatory response
	Topical corticosteroids	Broad-spectrum antiinflammatory activity
	Topical Calcineurin Inhibitors (TCIs)	Targeted antiinflammatory activity
	Oral immunomodulating agents (eg, azathioprine, cyclosporine, mycophenolate, etc) <sup>a</sup>	Systemic antiinflammatory activity
Infection	Phototherapy <sup>a</sup>	Proposed: antiinflammatory activity
	Topical/oral antiinfective agents	Treat cutaneous bacterial, fungal, or viral infections
	Bleach baths	Proposed: decrease microbial load on colonized and/or superinfected skin
Other	Antihistamines	Proposed: Sedating effect may aid in sleeping, indirectly decreasing night-time scratching and subsequent skin excoriation

<sup>a</sup> Reserved chiefly for severe and/or recalcitrant disease.

teria for hypoallergenicity and in AD diagnostic criteria), flaws in study designs (eg, lack of control for confounding factors, problems in blinding of study formula, and insufficient adherence to prescribed dietary avoidance protocols), the immunologic complexity of breast milk itself, and, possibly, genetic differences among patients that would affect whether breastfeeding is protective against the development of allergies or is, in fact, sensitizing.<sup>39,40</sup> In January 2008, the American Academy of Pediatrics Committee on Nutrition and Section on Allergy and Immunology published breastfeeding guidelines that replaced their previous policy statement.<sup>41</sup> The new committee concluded that there is a lack of evidence to support a major role in AD for maternal dietary restrictions during pregnancy or lactation. The committee also reported that for infants at high risk of developing atopic disease, exclusive breastfeeding for at least 4 months (compared with feeding intact cow milk protein formula) decreases the cumulative incidence of AD in the first 2 years of life; exclusive breastfeeding beyond this period did not seem to lead to additional benefit in the incidence of AD.<sup>42</sup> More long-term prospective studies are necessary before a consensus about breastfeeding recommendations can be reached.

#### Timing of Solid-Food Introduction

Zutavern et al<sup>43</sup> performed a large, population-based, prospective birth cohort study and concluded that there was no evidence to support a delayed introduction of solids beyond the sixth month of life on AD and atopic sensitization at 2 years of age. The findings were less clear when solids were introduced past the fourth month of life, and there was no evidence for a protective effect of a delayed introduction of solids on any outcome for children with atopic parents. The American Academy of Pediatrics Committee on Nutrition and Section on Allergy and Immunology published guidelines, in 2008, stating that there is no convincing evidence that delaying solid foods beyond 4 to 6 months of age has a significant protective effect on the development of atopic disease; this includes delaying introduction of those foods thought to be highly allergic such as cow milk, fish, eggs, and peanut-containing foods.<sup>42</sup> Additional

studies are necessary to document the long-term effect of dietary interventions on atopic disease.

#### Probiotics

As a result of greater understanding of immunologic reaction patterns in the skin, gut, and airways, there has been a resurgence of interest in probiotics. The findings to date on their utility in preventing or modifying AD, however, have been conflicting. A 2002 study by Rautava et al<sup>44</sup> revealed that the risk of developing AD during the first 2 years of life in infants was significantly reduced if the mothers had received probiotics during the 4 weeks before giving birth and during breastfeeding. All women within this study had a family history of atopy. More recently, however, a placebo-controlled study by Taylor et al<sup>45</sup> showed that early probiotic supplementation did not reduce the risk of AD in infants at high risk but, instead, was associated with increased allergen sensitization in those infants who were receiving supplements. The long-term significance of probiotics in the treatment of AD warrants additional investigation.

#### Skin Care

Excellent skin care is a traditional cornerstone of AD management. Although limited data exist to support the notion that emollients and moisturizers improve AD directly, these products are widely used because they improve the xerosis associated with AD (Table 4).<sup>46</sup> In general, ointments contain high concentrations of lipids and are generally more effective than creams or lotions, which are water-based and, therefore, may dry the skin somewhat after evaporation.<sup>6</sup> Ceramide-rich products are also useful for retaining moisture in the skin.<sup>47</sup> Recently, several novel barrier products have been cleared for marketing by the US Food and Drug Administration (FDA) as "510(k) medical devices" and contain ingredients that their manufacturers claim in addition to moisturizing may help to relieve pruritus, burning, and pain associated with AD; studies are underway to evaluate the utility of these new products and their potential role in helping to manage AD.<sup>48-51</sup>

With little evidence to recommend the use of one emollient over another, we support the adage that "a

good product applied works better than a more expensive product on the shelf." In other words, because emollients and moisturizers only work when they are actually used, patient and parental preference should be primary factors in selecting a daily emollient or moisturizer. In general, patients should use a dye-free, fragrance-free moisturizer and apply it at least twice per day subsequent to any topical pharmacologic therapies to allow active medications to reach the skin with full-effect.

### Bathing

The value of bathing remains somewhat controversial. The chief benefits of bathing are skin hydration and cleansing. Bathing may also improve penetration of topical therapies and may help debride infected eczema. The potential drawbacks of bathing are drying of the skin and disruption of the stratum corneum barrier during water evaporation, which can be minimized by using the "soak and seal" method.<sup>6,33</sup> With this technique, the child is bathed for several minutes in lukewarm water once or twice daily for mild or more severe AD, respectively. Use of a moisturizing cleanser is preferred, and highly fragranced soaps or bubble baths should be avoided. After bathing, caregivers should gently pat the child dry, being careful not to rub the skin with a towel, which can be thought of as "scratching in disguise." Liberal quantities of emollients should then be applied to maximize moisture retention.

### PHARMACOLOGIC TREATMENT OF ACUTE AD

Despite proper skin care and reasonable trigger avoidance, most children will experience a flare and require pharmacologic treatment. Flares of mild-to-moderate intensity are marked by itching, erythema, and excoriations, papules, and lichenification. More severe or major flares present with intense and persistent itching, substantial erythema, extensive excoriations, oozing/crusting, and lichenification. Two major classes of therapeutic agents are used for the treatment of AD: topical corticosteroids and topical calcineurin inhibitors (TCIs) (Table 4). Both classes of agents inhibit the associated inflammatory response, albeit through distinct mechanisms of action.

#### Topical Corticosteroids

Topical corticosteroids, the predominant AD therapy for more than 4 decades, provide effective flare control through their antiinflammatory, antiproliferative, immunosuppressive, and vasoconstrictive actions.<sup>52</sup> They suppress the release of inflammatory cytokines, and they act on a variety of immune cells including T lymphocytes, monocytes, macrophages, dendritic cells and their precursors.<sup>53</sup>

The current American system of classification stratifies topical corticosteroids into groups of roughly equal potency on the basis of the vasoconstrictor assay, with class I representing the most potent and class VII representing the least potent.<sup>54</sup> The difference in potency between classes is dramatic and is often misunderstood by both patients and their caregivers.<sup>52</sup> Very potent, class I preparations such as clobetasol propionate 0.05% are ~1800 times more potent than a class VII preparation

such as hydrocortisone ointment 1%.<sup>55</sup> The vasoconstrictor assay does not consider other factors that influence desired therapeutic effect and unwanted adverse effects: the state of the skin barrier, the body site involved, disease extent, the age of the patient, concomitant use of occlusion, the amount of steroid applied, and the duration of treatment. However, it does correlate well with clinical efficacy and provides a reasonable guide to the potential for adverse effects.

Tolerability and safety concerns regarding topical corticosteroids are well known and include local adverse effects such as skin atrophy, striae, telangiectasias, hypopigmentation, rosacea, perioral dermatitis, acne, cataracts, and glaucoma; these local adverse effects can occur more frequently when topical corticosteroids are used on sensitive areas of thin skin, such as the face, neck, or groin. Systemic adverse effects such as hypothalamic-pituitary-adrenal axis suppression (Table 5), growth retardation in children, and reduced bone density have also been documented.<sup>1</sup> A recent review of topical therapies for AD showed, however, that although some systemic exposure to these topical agents does occur, physiologic changes seem to be uncommon and systemic complications rare when medications are used properly.<sup>56</sup> Also of concern is the risk of flare relapse after discontinuation of treatment and, rarely, steroid insensitivity. "Steroid phobia" among caregivers is common, and suboptimal use of topical corticosteroids as a result of concerns about adverse effects can be impediments to effective management.<sup>33,52</sup> It is important to anticipate these concerns and stress that, despite these well-known potential adverse effects, topical corticosteroids remain the first-line treatment for atopic flares in the pediatric population.

The extensive use of topical corticosteroids in clinical practice is supported by an ever-expanding body of clinical trial data, which help to provide physicians with sensible recommendations for the quantity, frequency, and duration of topical corticosteroid therapy.<sup>56,57</sup> Even with these recommendations, variation in topical steroid prescribing habits among dermatologists is common.<sup>58</sup> Some clinicians opt to begin treatment with a more potent preparation to induce remission, followed by a relatively quick tapering down of preparation potency as the AD improves; a subsequent stepwise model allows for as-needed management based on disease activity. A second approach is to use short bursts of a potent preparation followed by a steroid-free "holiday period" of emollient use only until relapse occurs.<sup>1,33,52</sup> Another treatment regimen relies on more prolonged continuous treatment with less-potent preparations. Regarding dosage frequency, 1 large systematic review revealed that using twice-daily applications of topical corticosteroids was no more effective than once-daily application.<sup>57</sup> Ultimately, providers should consider drug-specific FDA indications when educating and instructing patients on topical corticosteroid usage.

#### Topical Calcineurin Inhibitors

The 2 currently approved TCIs, tacrolimus and pimecrolimus, provide an alternative to topical corticosteroids and are approved by the FDA as second-line agents for the

**TABLE 5 Select Topical Corticosteroids and Their Hypothalamic-Pituitary-Adrenal Axis Suppression Studies: Pediatric Experience**

Class	Steroid	Vehicle	Dosage and Frequency	Age Group	Design	Duration of Test	HPA Studies	Source
VII	Hydrocortisone 1%	Ointment	48.7–223.2 mg/m <sup>2</sup> BSA per d; 9 of 14 also intermittently used moderate-potency preparations	3.1 to 10.7 y	n = 14; moderate or severe AD; 58% median BSA affected	3 to 10 y (median: 6.5 y)	PC: no change in basal/peak plasma levels but earlier peak seen in patients with AD versus controls	Patel et al <sup>98</sup>
VII	Hydrocortisone 2.5%	Ointment	2 times per d		n = 20; open label, parallel	4 wk	CST: all normal	Lucky et al <sup>99</sup>
VI	Alclometasone dipropionate 0.05%	Cream	2 times per d		n = 39; open label	3 to 4 wk	PC (AW): all normal	Crespi <sup>100</sup>
VI	Desonide 0.05%	Hydrogel	2 times per d	6 mo to 6 y	n = 40; open label; moderate-to-severe AD; 51% mean BSA affected	4 wk	CST: normal in all patients without protocol violations; 1 of 3 abnormal in patients with protocol deviations	Eichenfield et al <sup>101</sup>
VI	Fluocinolone acetonide 0.01%	Protein-free peanut oil	2 times per d	Study 1: 3 mo to 2 y; study 2: 2 to 12 y	Study 1: n = 24, open label, moderate-to-severe AD, ≥20% BSA affected; study 2: n = 32, open label, moderate-to-severe AD, ≥50% BSA affected	4 wk	CST: all normal	Study 1: On file with the FDA <sup>102</sup> ; study 2: Paller et al <sup>103</sup>
V	Fluticasone propionate 0.05%	Cream	2 times/d (average amount of drug used per d: 3.8 g for ages 3–35 mo, 7.7 g for ages 36–70 mo)	3 mo to 6 y	n = 43; open label; moderate to severe AD; 64% mean BSA treated	3 to 4 wk	CST: 2 of 43 patients with abnormal test results; 1 patient with 95% BSA affected normalized 12 d after last study dose; 1 patient with 35% BSA was lost to follow-up	Friedlander et al <sup>104</sup>
V	Fluticasone propionate 0.05%	Lotion	2 times per d	3 mo to 6 y	n = 42; open label; moderate-to-severe AD; 65% mean BSA treated	3 to 4 wk	CST: all normal	Hebert et al <sup>105</sup>
V	Prednicarbate 0.1%	Cream	2 times per d	4 mo to 12 y	n = 55; open label; mostly moderate-to-severe AD (1 "mild" enrolled); 46.7% mean BSA affected	3 wk	CST: all normal	Moshang <sup>106</sup>
IV	Mometasone furoate 0.1%	Cream	1 time per d	6 to 23 mo	n = 97; open label; AD (severity not stated); 41% mean BSA affected	3 wk	CST: 16% of patients with abnormal tests (4 of 5 tested patients normalized 2–4 wk after treatment)	On file with the FDA <sup>107</sup>
III	Fluticasone propionate 0.005%	Ointment		n = 35; AD (severity not stated); ≥35% BSA affected	3 to 4 wk	3 to 4 wk	CST: 4 patients with abnormal test results	On file with the FDA <sup>108</sup>
III	Triamcinolone acetonide 0.1%	Ointment	4 times per d (average amount of drug used per d: 13–46 g/m <sup>2</sup> )	7 mo to 8 y	n = 7; open label; severe AD	6 wk	PC (AW/PW): "no substantial difference" 24-HUC: "no notable depression"	Rasmussen <sup>109</sup>
II	Mometasone furoate 0.1%	Ointment	1 time per d	6 to 23 mo	n = 63; open label; AD (severity not stated); 39% mean BSA affected	3 wk	CST: 27% of patients with abnormal test results (5 of 8 tested patients normalized 2–4 wk after treatment)	On file with the FDA <sup>110</sup>

**TABLE 5** Continued

Class	Steroid	Vehicle	Dosage and Frequency	Age Group	Design	Duration of Test	HPA Studies	Source
I	Fluocinonide 0.1%	Cream	1 or 2 times per d	Cohort 1: 12 to <18 y; cohort 2: 6 to <12 y; cohort 3: 2 to <6 y; cohort 4: 3 mo to <2 y	n = 126; open label; moderate-to-severe AD; mean BSA affected ranged from 34% (cohort 1, twice daily) to 43% (cohort 4, once daily)	2 wk	CST: cohort 1: 1 of 15 patients in twice-daily group with abnormal test results (normalized 2 wk after treatment); cohort 2: 2 of 16 patients in twice-daily group with abnormal test results (1 normalized 8 d after treatment, and 1 normalized 2 wk after treatment); cohort 3: 1 of 15 patients in twice-daily group with abnormal test result (suspected collection error; not suppressed)	Schlessinger et al <sup>111</sup>
I	Clobetasol propionate 0.05%	Lotion	2 times per d	12 to 17 y	n = 14; moderate-to-severe AD; ≥20% BSA affected	2 wk	9 of 14 patients with adrenal suppression (assessment method not stated)	On file with the FDA <sup>112</sup>

HPA indicates hypothalamic-pituitary-adrenal; BSA, body surface area; PC, plasma cortisol; CST, Cosyntropin; 24-HUC, 24-hour urinary cortisol.

short-term and noncontinuous chronic treatment of moderate-to-severe AD in immunocompetent patients aged  $\geq 2$  years.<sup>59,60</sup> TCIs block the production and release of proinflammatory cytokines after antigen-specific or nonspecific activation of T cells and mast cells.<sup>61,62</sup>

The safety and efficacy of tacrolimus and pimecrolimus have been demonstrated in several short-term (6-week) and long-term (>2-year) clinical trials.<sup>63–65</sup> Data from clinical trials have shown that pimecrolimus reduces the number and severity of flares, extends the length of time between major flares, and decreases pruritus and other cutaneous signs associated with AD.<sup>66</sup> Likewise, long-term, intermittent (once-daily, 3-times-weekly) maintenance use of tacrolimus ointment in patients with stabilized AD has been shown to significantly increase time between disease exacerbation and total number of disease-free days versus vehicle.<sup>67</sup> The incidence of adverse effects (mostly transient application-site stinging) is generally low.<sup>68,69</sup>

In January 2006, the FDA added a boxed warning to TCI labels noting that the long-term safety of these agents has not been established. The warning was added in response to widespread off-label use in the infant population (<2 years of age) and concerns about a potential cancer risk based on 3 factors: (1) a shared mechanism of action with systemic calcineurin inhibitors; (2) animal toxicology studies; and (3) rare postmarketing case reports of malignancy (skin cancer and lymphomas). It is important to note that none of the reported lymphomas were characteristic of the posttransplant lymphoproliferative disease type observed with systemic immunosuppression.<sup>59,60</sup> Clinical studies have indicated minimal systemic absorption and, considered together, the available data do not suggest that the use of TCIs is associated with systemic immunosuppression, impacts the delayed-type hypersensitivity response, or has an increased association with skin cancer.<sup>65,70,71</sup>

Accordingly, the FDA has not requested that ongoing studies with TCIs in pediatric patients be halted. Official indications for use, however, were changed from “short-term and intermittent long-term therapy in the treatment of patients with moderate to severe AD in whom the use of alternative, conventional therapies are deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or are intolerant of alternative, conventional therapies” to the current indication of “second-line therapy for the short-term and noncontinuous chronic treatment of moderate to severe AD in nonimmunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for AD, or when those treatments are not advisable” in children aged  $\geq 2$  years.<sup>59,60</sup>

TCIs may be particularly valuable for patients with AD in whom the clinical course is marked by disease persistence and/or frequent flares, which would otherwise result in an almost continuous need for topical corticosteroid treatment. TCIs may also be of significant benefit for those patients affected in sensitive skin areas such as around the eye, face, neck, and genital area, where systemic absorption and the risk of skin atrophy

are of special concern. The safety data for TCIs in the pediatric population are still accumulating and will be helpful in guiding physicians in the use of these particular agents.

### TOPICAL CORTICOSTEROID AND TCI USE IN DISEASE MANAGEMENT

Both acute flare treatment and overall disease management must be tailored to the individual patient, and disease severity (including disease persistence and frequency of flares) must be considered. Recognizing the risk/benefit profile of both topical corticosteroids and TCIs allows for optimal individualized patient care using a sliding disease/treatment scale or stepwise therapeutic approach.<sup>72</sup> We have adopted the use of short-term bursts of mid- to high-potency topical steroids, typically applied twice daily for 7 to 10 days (versus the long-term use of less-potent agents), followed by a close reexamination of the patient, as part of our current treatment approach for children with rapid flares. After achieving control of a flare, we shift therapy to a less-intense treatment and focus on a maintenance regimen with moisturization (optimally, at least twice daily) at its core. If a topical corticosteroid has been used to treat a flare, it can be tapered to a lower-potency agent and from daily to intermittent (eg, thrice- or twice-weekly) application.<sup>6</sup> Patients with a history of flare recurrence after discontinuation or tapering of topical corticosteroids may benefit from transition to TCI therapy at that point.<sup>3,67</sup> Some physicians advocate the use of TCI monotherapy to control flare recurrence while limiting patients' long-term exposure to corticosteroids.<sup>72</sup>

Irrespective of treatment strategy, physicians should monitor patient progress and disease course regularly (eg, evaluations at 2, 6, and 12 weeks) and evaluate the efficacy and tolerability of therapy. This evaluation should include an assessment of medication use (eg, type, quantity applied, refills made, etc), which allows the physician to gauge compliance and medication risks. The fingertip unit (FTU), defined as the amount of topical medication extending from the tip to the first joint on the palmar aspect of the index finger, is a guideline for estimating the amount of topical medication needed to cover a given area: it takes ~1 FTU to cover the hand or groin, 2 FTUs for the face or foot, 3 FTUs for an arm, 6 FTUs for the leg, and 14 FTUs for the trunk.<sup>73</sup>

### Adjunctive Therapy

Pruritus is one of the defining features of AD, with associated scratching that leads to excoriated, often superinfected lesions, bleeding, lichenification, and/or nodular changes. In addition, pruritus can cause significant sleep disturbance and affect the patient's and caregiver's quality of life.<sup>74</sup> Identifying and removing triggers of pruritus is appropriate. Although they do not have direct effects on the pruritus associated with AD, sedating systemic antihistamines such as hydroxyzine and diphenhydramine may be useful for improving sleep in patients with flare-ups. This practice has not been

evaluated rigorously in large, randomized, double-blind, placebo-controlled trials, and the drowsiness that may be associated with daytime use is a legitimate concern for school-aged children.<sup>75,76</sup> Second-generation antihistamines are less useful in managing AD, but they may benefit patients with allergic triggers and, with chronic use, may help decrease the rate of atopic disease.<sup>77-79</sup> Doxepin, a tricyclic antidepressant with anxiolytic effects, has the highest H1-receptor antagonist activity among the tricyclic antidepressants and is the most sedating. It is generally reserved for patients with severe AD and has an adverse-effect profile that includes daytime sedation, hypotension, and tolerance.<sup>80</sup>

### Antimicrobial Agents

AD lesions provide a favorable environment for bacterial colonization and proliferation, and *Staphylococcus aureus* can be isolated in up to 90% of AD skin lesions.<sup>11</sup> This high prevalence of colonization is most likely multifactorial; proposed mechanisms include increased adherence of bacteria to inflamed skin, defective skin barrier function, decreased innate antibacterial activities, reduced immune responses against bacteria, and skin-surface pH changes toward alkalinity.<sup>81</sup> Patients with AD can have sudden exacerbations of AD attributable to overgrowth of *S aureus* that can be independent of true secondary bacterial infection, a notion supported by the clinical response of patients with severe AD to anti-staphylococcal antibiotics.<sup>82,83</sup> Honey-colored crusting, folliculitis, and pyoderma are signs of overt infection, and topical and/or oral antibiotic therapy, typically of short duration to avoid the development of bacterial resistance, is indicated.<sup>1,6</sup> Obtaining skin cultures should be considered before treatment, because methicillin-resistant *Staphylococcus aureus* may be an important pathogen in some patients. Recurrent, deep-seated *S aureus* infections should raise the possibility of an immunodeficiency syndrome such as hyper-IgE syndrome.<sup>11</sup> Diluted bleach baths (Table 6), analogous to swimming in a chlorinated pool, are an adjuvant anti-infective treatment that can help decrease the number of local skin infections and reduce the need for systemic antibiotics for patients with AD with heavily colonized and/or superinfected skin.<sup>84</sup>

Patients with AD are also prone to recurrent viral infections, perhaps because of local defects in T-cell function. *Molluscum contagiosum*, a common cutaneous viral infection, may often manifest as small, dome-shaped papules that characteristically show a central umbilication. They typically affect the trunk, axillae, antecubital and popliteal fossae, and crural areas. Lesions tend to be most numerous at sites of active dermatitis and can induce pruritus as well as dermatitis around the *Molluscum* papules.<sup>25</sup> Eczema herpeticum, also known as Kaposi's varicelliform eruption, is a serious risk in patients with widespread AD and may be easily misdiagnosed as bacterial superinfection.<sup>85</sup> After an incubation period of 5 to 12 days, these patients can present with multiple, itchy, vesiculopustular, disseminated lesions and painful, "punched-out" erosions that

**TABLE 6 A Bleach Bath Primer**


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Explain to patients that their skin may benefit from “swimming in pool water.” Then, give them these instructions for making a pool right in their very own bathroom.

Add lukewarm water to fill the tub completely (about 40 gallons of water).

Depending on the size of the tub/amount of water used, add ¼ to ½ cup of common bleach solution to the bath water. Any sodium hypochlorite 6% solution will do (for example, Chlorox liquid bleach); the goal is to make a modified Dakin’s solution with a final concentration of about 0.005%.

Stir the mixture to ensure that the bleach is completely diluted in the bath water.

Have patients soak in the chlorinated water for 5 to 10 minutes.

Thoroughly rinse skin clear with lukewarm, fresh water at the end of the bleach bath to prevent dryness and irritation.

As soon as the bath is over, pat the patient dry. Do not rub dry, as this is the same as scratching.

Immediately apply any prescribed medications/emollients.

Repeat bleach baths 2–3 times a week or as prescribed by the physician.

The following restrictions apply

Do not use undiluted bleach directly on the skin. Even diluted bleach baths can potentially cause dryness and/or irritation.

Do not use bleach baths if there are many breaks or open areas in the skin (for fear of intense stinging and burning).

Do not use bleach baths in patients with a known contact allergy to chlorine.

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fail to respond to oral antibiotics.<sup>11</sup> Before treatment, herpes infection should be documented (via culture and/or direct fluorescent antibody), and antiviral therapy should be initiated as soon as possible. Similarly, eczema vaccinatum is a severe, potentially fatal widespread eruption caused by the live-virus smallpox vaccination or even exposure to vaccinated people such as military personnel who receive smallpox vaccination in preparation for overseas deployment.<sup>86</sup> For this reason, smallpox vaccination is contraindicated for patients who have ever been diagnosed with AD, even if the condition is not currently active. In addition, persons with household contacts who have a history of AD, irrespective of disease severity or activity, should not be vaccinated.<sup>87</sup> Fungal infections such as those caused by *Trichophyton rubrum* are also more common in patients with AD. Antifungal therapy has been shown to reduce the severity of AD lesions exacerbated by *Malassezia furfur*, particularly in the seboreic areas of the skin and scalp.<sup>11</sup>

### Wet Wraps

Patients with severe AD or disease that is refractory to standard topical treatment may require the use of wet

wraps (Table 7), which were first touted as a relatively safe and effective treatment >20 years ago.<sup>88</sup> Although time consuming, wet wraps can be a useful tool in the intensive treatment of AD. Wet wraps increase skin hydration and serve as an effective barrier to scratching, which helps promote more restful sleep. Likewise, they act as an occlusive barrier that promotes penetration of topical corticosteroids into the skin, thereby increasing the amount of medication delivered to the affected areas of inflammation. A recent review of the literature revealed a wide variety in wet-wrap methodology. On the basis of currently available evidence, the authors of the study found wet wraps with once-daily application of topical corticosteroids to be an efficacious and safe short-term intervention for children with severe and/or refractory AD; temporary systemic bioactivity of the corticosteroids was the only reported serious adverse effect.<sup>89</sup> Wet wraps may cause maceration of the skin and secondary infections if overused or used incorrectly. Paradoxically, they may promote skin dryness if sufficient emollients are not part of the regimen.<sup>90</sup> Because of these concerns, it is imperative that patients be supervised closely by a physician who has expertise in the use of wet wraps.

**TABLE 7 Keeping Eczema Under Wraps: Recommendations for Applying Wet Wraps**


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Gather your supplies.

Topical steroid ointment and/or emollient prescribed by your physician.

The wraps themselves consist of a bottom (wet) and top (dry) layer. Gauze wrap (eg, Kerlex) or cotton sleepers, pajamas, or long johns may be used. It will be necessary to have two of the material chosen. Alternatively, it is possible to use the “daddy sock” method for wrapping extremities. Simply cut a small hole in the toes of any adult-sized pair of 100% cotton socks to create a pair of tubular cotton bandages that fit easily over an extremity, can be moved up or down as needed, and can be washed and reused.

Warm water in a sink or a basin.

Apply the steroid ointment directly to the patient’s inflamed skin using tongue depressors or popsicle sticks (similar to how a spatula is used in cooking). Using a “spatula” helps to avoid direct contamination of the medication supply, allows large areas to be covered quickly and evenly, and prevents the caregiver from being unnecessarily exposed to topical corticosteroids.

Apply emollient to the rest of the patient’s skin.

Take a layer of the wrap (e.g., gauze or one sock) and soak it in warm water.

Wring out any excess water until this bottom wet layer is only very slightly damp.

Wrap the affected area with the wet layer material. Make sure the wet layer is not too tight.

Immediately put the dry layer over the wet layer. Do not use plastic as the dry layer (it is too occlusive and may be a choking hazard).

Make sure the wrapped patient remains in a warm environment, which helps to promote a higher degree of humidity and ensures that the child does not get too cold as the evaporation process occurs.

Wet wraps are generally left in place overnight and may be applied for 5 to 7 days in a row. As always, follow the advice of the physician for frequency of change and duration of use.

Maintain close contact with the physician while undergoing the use of wet wraps. Report any suspected adverse effects immediately.

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## Systemic Therapies

Systemic immunomodulatory therapies such as phototherapy, cyclosporine, azathioprine, and mycophenolate have gained acceptance in recent years as treatment for refractory AD that does not respond to topical therapies.<sup>91</sup> Phototherapy, which evolved as a treatment for AD on the basis of the observation that many patients' conditions seem to improve during the summer months with increased exposure to natural light, has been shown to be an effective modality. Multiple treatments are usually required to be effective, but they can be inconvenient for patients and their families depending on location and accessibility to a suitable light source. Adverse effects can include erythema, pruritus, and pigmentary changes. Likewise, UV light is known to cause premature skin aging and cutaneous malignancies.<sup>90</sup> Although further study in the pediatric population is necessary, it seems that phototherapy is a valuable and safe therapeutic option for selected children whose conditions do not respond to other treatments.<sup>92</sup> Cyclosporine may be used as a short-term treatment or as a bridge between other steroid-sparing alternatives. The safety and efficacy of cyclosporine in the treatment of adult and childhood AD is well documented, although hypertension and renal toxicity are limitations to long-term therapy.<sup>93</sup> Azathioprine, dosed according to thiopurine methyltransferase genotype/levels, is also an effective monotherapy; blood cell counts and liver function tests should be monitored closely, and drug hypersensitivity and gastrointestinal disturbances have been reported.<sup>94–96</sup> Mycophenolate mofetil, an inhibitor of purine synthesis, has a good safety profile and represents a promising therapeutic alternative for severe, refractory AD; additional prospective controlled studies in a pediatric population are needed.<sup>97</sup>

## Specialty Referrals

Because AD is a problem of skin barrier dysfunction and inflammation, the primary focus of management should be on comprehensive management of skin care and barrier repair. Referral to a pediatric dermatologist may be helpful in this regard. Likewise, consider referring those patients with a diagnosis of moderate or severe AD; those whose conditions are unresponsive to standard treatments (including moderate-potency topical corticosteroids); those with persistent disease and/or frequent flares; those patients who have been hospitalized as a direct consequence of their AD; and those patients who require systemic therapies for flares and/or maintenance. In general, allergy testing is not a first-line referral recommendation in the routine evaluation and treatment of uncomplicated AD.<sup>11</sup> Consultation with an allergist can be useful, however, when proper skin care is not working or when the clinical picture hints strongly at specific triggers. Referral to immunology or gastroenterology is warranted, respectively, if underlying systemic infections are frequent or when eosinophilic gastroenteritis/esophagitis becomes a concern in younger children with concomitant failure to thrive.

## CONCLUSIONS

AD is a common, chronic skin disease that starts early in life and can adversely affect a child's overall health and development. Topical corticosteroids remain the cornerstone of therapy, and recent studies continue to help assuage concerns about potential long-term adverse effects, especially in young children. TCIs have been shown to provide an effective, steroid-sparing alternative for appropriate patients, particularly those who are prone to frequent flares and need AD treatment in sensitive skin areas. In conjunction with these pharmacologic treatments, overall management depends on (1) educating caregivers about AD's chronic, unpredictable course characterized by flares that can occur despite best efforts, (2) appreciating the compromised epidermal barrier and the importance of proper skin care, (3) approaching trigger avoidance carefully and with the understanding that, in general, AD is a multifactorial disease, and (4) using a team-oriented approach that includes primary care physicians, specialists, nurses, psychologists, behavioral therapists, and other health care professionals to better achieve long-term success for patients with AD.

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## SCIENTISTS FIND WAY TO CREATE RED BLOOD CELLS

“New York—Scientists say they’ve found an efficient way to make red blood cells from human embryonic stem cells, a possible step toward making transfusion supplies in the laboratory. The promise of a virtually limitless supply is tantalizing because of blood-donor shortages and disappointments in creating blood substitutes. Red blood cells are an important component of blood because they carry oxygen throughout the body. Experts called the new work an advance, but cautioned that major questions had yet to be answered. The research, published online Tuesday by the journal *Blood*, was reported by scientists at Advanced Cell Technology in Worcester, Massachusetts, the University of Illinois at Chicago and the Mayo Clinic in Rochester, Minnesota. The researchers said the cells they made behaved like natural red blood cells in lab tests, and that their process could be used in large-scale production. The results suggest that embryonic stem cells could someday supply type O-negative ‘universal donor’ red cells for transfusion, they wrote.”

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Noted by JFL, MD