Clinical Therapeutics for Atopic Dermatitis and Fungal Infections: An Update

Topical Steroids in Pediatric Atopic Dermatitis

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Topical Antifungals: An Update

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TARGET AUDIENCE

This activity is intended for health care professionals, including dermatologists and pediatricians, who are involved in the treatment of patients with atopic dermatitis.

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Topical Steroids in Pediatric Atopic Dermatitis

Leon H. Kircik, MD

Recent epidemiologic data show that more than 15 million individuals in the United States have atopic dermatitis (AD). In the majority of patients, AD peaks in the first years of life; almost 50% of patients with AD are 12 years of age or younger. An estimated 40% continue to experience AD symptoms into adulthood.

The data also show a trend toward an increasing prevalence of AD in children. The environmental changes may contribute qualitatively or quantitatively to antigen exposures, which can trigger the disease.

The High Costs of AD

Direct costs include payments for over-the-counter treatments and therapies that are not covered by insurance (for example, allergy testing and alternative therapies). However, most of the financial burden of AD results from indirect costs. These include losses to employers of parents of children with AD; for example, if a child cannot go to school, a parent may not be able to go to work. Lost productivity attributed to AD is estimated at $619 million yearly, including $183 million in lost workdays. Since AD primarily affects children, the majority of productivity losses is due to caregiver lost workdays, amounting to $249 million. The remaining $188 million is attributable to restricted activity days due to AD.

In addition to monetary costs, AD substantially affects quality of life (QOL). QOL issues include itching, sleeplessness, poor work functioning, and decreased coping skills at work and at home.

Goals and Options for Treatment in Children

There are four recognized objectives for the treatment of AD in children (summarized in Table 1): education, induction of remission, maintenance, and rescue of flares.

EDUCATION

Parents and older children must understand the value of emollients (as discussed below under “Maintenance Therapy”) and should know the proper techniques for bathing and emollient application.

In addition, parents and patients should be informed about allergens. It is advisable to avoid known or suspected allergens, despite the fact that allergen avoidance currently has no established role in the management of patients with AD.

An evidence-based review of food allergy and dust-mite avoidance strategies for established AD failed to demonstrate the therapeutic value of food avoidance (except, perhaps, the avoidance of eggs in infants). Tan and colleagues conducted a study of house-dust-mite reduction measures and concluded that these measures may benefit children with AD, but other studies have failed to produce definitive evidence that reducing dust mites can improve AD.

INDUCTION OF REMISSION

The use of topical corticosteroids have long been recognized as key elements in regimens designed to induce remission of AD. Topical corticosteroids are discussed in detail in the following section.

In addition to these measures, patients should be monitored for skin infections and appropriate antimicrobial therapy should be used as indicated. In particular, it is important to recognize the role of *Staphylococcus aureus* in disease flares. *S. aureus* colonizes the skin of most patients with AD. Topical antibiotics and anti-inflammatory therapy usually are effective for limited infections. Patients with widespread infections or severe flares often respond to oral antibiotics.

The use of longer courses of oral antibiotics is not recommended because of the increased prevalence of methicillin-resistant strains of *S. aureus*. Bacterial cultures and surveillance of family members are advisable prior to treatment of patients with recurrent infections so that the appropriate antimicrobial therapy and environmental protection strategies can be implemented.

MAINTENANCE THERAPY

Emollients have long been recognized as, and remain the foundation for, effective maintenance therapy and the prevention of relapse. The purpose of emollient applications is the optimization of skin barrier function. In general, emollient formulations with greater concentrations of lipids provide a more effective barrier than water-based products. In fact, some recent studies have explored the possible benefits of including stratum corneum lipids in emollients. The results of one uncontrolled study, using an emollient containing the stratum corneum lipid ceramide, showed benefit over routine emollient therapy.

Topical corticosteroids are the cornerstone for acute control of flares, but have not been considered safe for long-term maintenance. However, intermittent therapy—for example, twice-weekly applica-

Table 1. Objectives for Treating AD in Children

<table>
<thead>
<tr>
<th>Education: importance of emollients and avoidance of triggers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction of remission:</strong> topical corticosteroids, treatment of infection as needed</td>
</tr>
<tr>
<td><strong>Maintenance:</strong> barrier creams, emollients, topical corticosteroids twice weekly, topical calcineurin inhibitors</td>
</tr>
<tr>
<td><strong>Rescue of flares:</strong> topical corticosteroids ultraviolet light, methotrexate, cyclosporine</td>
</tr>
</tbody>
</table>

AD = atopic dermatitis.

Source: Courtesy of Leon H. Kircik, MD
Topical calcineurin inhibitors have been shown to be safe and effective for long-term maintenance in children with AD. In one 4-year study of tacrolimus, Hanifin and colleagues reported that use of this agent was safe and effective in children with moderate and severe AD. A 1-year study of pimecrolimus by Wahn et al demonstrated that chronic use of this agent reduced both the number of flares and the amount of corticosteroids required when treatment was initiated at the first signs or symptoms of AD activity.

RESCUE OF FLARES

Aggressive treatment is indicated for flares, and the strategy is the same as that for inducing remission. In addition, whenever possible, the underlying trigger for a flare should be determined. These include bacterial or viral infections, dry skin, psychological stress, and noncompliance with maintenance therapy. The benefits of phototherapy in the control of AD are well recognized. Modalities include treatment with ultraviolet A (UVA), UVB, and psoralen with UVA light (PUVA). Narrow-band UVB phototherapy is preferred by many for maintenance therapy in patients with moderate-to-severe disease that does not respond to maintenance treatment with topical agents.

The use of oral corticosteroids is indicated when intensive treatment with topical agents fails. When a flare cannot be controlled with topical corticosteroids and phototherapy, oral cyclosporine may be considered in patients in whom its use is not contraindicated. (The reader is referred to Akhavan and Rudikoff for a discussion of clinical guidelines for the use of cyclosporine in AD.)

Other systemic therapies that have been used to manage AD flares include azathioprine, mycophenolate mofetil, methotrexate, and interferon-α. Efficacy studies have provided support for the use of these agents in appropriate circumstances. However, no evidence has been published supporting the use of antihistamines and leukotriene inhibitors in AD, although these are commonly and widely used for such therapy. Antihistamines with sedative effects may be useful during a flare, not because of any effects of AD symptoms, but mild sedation may help patients (and their caregivers) sleep better.

### Table 2. Topical Corticosteroid Needed to Achieve a Concentration of 2.0 mg/cm²

<table>
<thead>
<tr>
<th>Age</th>
<th>Total Body</th>
<th>Hands</th>
<th>Feet</th>
<th>Each Leg</th>
<th>Each Arm</th>
<th>Chest</th>
<th>Back</th>
<th>Face</th>
<th>Scalp</th>
<th>Groin &amp; Buttocks</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>0.5 kg</td>
<td>25 g</td>
<td>35 g</td>
<td>50 g</td>
<td>35 g</td>
<td>60 g</td>
<td>60 g</td>
<td>45 g</td>
<td>45 g</td>
<td>30 g</td>
</tr>
<tr>
<td>6 years</td>
<td>1 kg</td>
<td>50 g</td>
<td>70 g</td>
<td>140 g</td>
<td>70 g</td>
<td>130 g</td>
<td>130 g</td>
<td>65 g</td>
<td>65 g</td>
<td>60 g</td>
</tr>
<tr>
<td>12 years</td>
<td>1.6 kg</td>
<td>80 g</td>
<td>110 g</td>
<td>230 g</td>
<td>110 g</td>
<td>200 g</td>
<td>200 g</td>
<td>90 g</td>
<td>90 g</td>
<td>100 g</td>
</tr>
<tr>
<td>Adult</td>
<td>2.3 kg</td>
<td>120 g</td>
<td>160 g</td>
<td>375 g</td>
<td>160 g</td>
<td>300 g</td>
<td>300 g</td>
<td>80 g</td>
<td>80 g</td>
<td>135 g</td>
</tr>
</tbody>
</table>

*Applied twice daily for 1 month.

HPA-axis function returns to normal when use of the drug is discontinued. Desonide hydrogel is another formulation of this drug, which also has FDA approval for use in children down to 3 months of age. HPA-axis suppression was shown in one out of 37 patients in a clinical trial. (Although the labeling states an association with HPA-axis suppression, it may be that this finding actually was the result of a technical problem the investigators had in drawing blood from this one patient.)

Another newly approved agent, a 0.05% lotion formulation of fluticasone propionate, is indicated for once-daily application for patients down to 1 year of age and is not associated with HPA-axis suppression. Eichenfield and colleagues16 conducted two separate but parallel randomized, double-blind, placebo-controlled studies. A total of 438 subjects with moderate to severe disease participated, ranging in age from 3 months to 16 years. (The demographics and other characteristics were similar in the two studies, referred to as Study A and Study B.)

Weekly assessments were made of the patients’ head and neck, trunk, arms, and legs. For each body site, the investigators estimated the BSA affected and assessed the severity of five key signs and symptoms: erythema, scaling, infiltration/papulation, erosion/oozing/crusting, and pruritus. A physician’s global assessment (PGA) scale was used to score changes in severity of these five signs and symptoms from baseline to the end of the 4 weeks of treatment.

The primary end points that determined overall treatment success were ≥50% clearance of lesions plus improvement or no change in ≥75% of the 20 symptom assessments on PGA. Primary end points on additional analysis (ie, not planned analysis) were ≥50% clearance of lesions plus improvement or no change in 100% of the 20 symptom assessments; the findings from the planned analysis were confirmed by those of the additional analysis.

In Study A, ≥50% clearance of lesions on PGA was significantly higher with fluticasone propionate lotion (n=73) than with vehicle (n=29) (P<0.001). Subjective assessments by the subjects/parents in Study A indicated that 50% in the active treatment group rated their response as excellent, compared with 15% who used vehicle only (P<0.001). The differences in Study B were similar and also statistically significant: excellent responses were reported by 48% of patients who received fluticasone, compared with 7% of the patients who received vehicle (P<0.001).

The most common adverse effects were burning and stinging, reported by 4% of patients who received fluticasone and 5% of subjects in the control group. The lack of difference between the two groups is not surprising; many patients with AD have burning and stinging in response to the application of almost any topical agent. This formulation has a cosmetically acceptable, emollient-rich vehicle that spreads easily, even in hair-bearing areas.

**Summary**

AD remains one of the most common diseases seen in dermatologists’ offices. Improvements continue to be made in topical corticosteroids, particularly those tested specifically in pediatric populations; examples are the new formulations of desonide (in foam and hydrogel vehicles) and of fluticasone propionate (a lotion vehicle). These new agents are FDA-approved and appropriate for use in children.

**References**

The species of fungi that infect the skin in humans—that is, the dermatophytes—are yeasts and the fungi imperfecti (also called deuteromycota), including epidermophytons, microspora, and trichophytons. The incidence and characterization of dermatophytic infections in the United States have been difficult to estimate because data are available only on patients who seek treatment for their conditions. A casual survey of pharmacy shelves reveals a large number of over-the-counter topical antifungal medications available for self-treatment by patients with a variety of dermatophytic infections (in most cases, self-diagnosed). Unless these infections persist or become more severe, self-treating patients are not likely to seek professional medical help.

Gupta and Cooper conducted a statistical study of the incidence of dermatophytic infections in the United States, analyzing data from the National Ambulatory Medical Care Survey (1990-1999). According to their report, dermatophytic infections, a wide-spectrum agent is preferred, ideally one that is active against both yeast and dermatophytes. Ciclopirox is the first topical antifungal agent butenafine was FDA approved in 1992, 1992, and 2001, respectively. Most recently, in 2004, the FDA approved ciclopirox olamine, the first antifungal in a new class called hydroxypyridones.

### Table. Topical Antifungals Available in the United States

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000s &gt;</td>
<td>Hydroxypridone</td>
<td>Ciclopirox olamine 2004</td>
</tr>
<tr>
<td>1980s &gt;</td>
<td>Amines: allyl/benzyl</td>
<td>Terbinafine 1992</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Butenafine 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nafitine 1988</td>
</tr>
<tr>
<td>1970s &gt;</td>
<td>Azoles</td>
<td>Econazole 1982</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ketoconazole 1985</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clotrimazole 1993</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sertaconazole 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxiconazole 1988</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Miconazole 1974</td>
</tr>
<tr>
<td>1950s &gt;</td>
<td>Polyenes</td>
<td>Nystatin 1976</td>
</tr>
<tr>
<td>Other</td>
<td>Amphotericin B</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Selenium sulfide</td>
<td>1975</td>
</tr>
<tr>
<td></td>
<td>Sulfacetamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tolnaftate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Undecylenic acid</td>
<td></td>
</tr>
</tbody>
</table>

**Source:** Courtesy of Douglas W. Kress, MD, and Shay Jones, PA-C, MEd, MPH

**INDICATIONS AND MECHANISMS OF ACTION**

Amphotericin B is not approved as a topical agent and is rarely used in the United States. Nystatin, also in the polyene class, is approved for the treatment of yeast infections caused by Candida species. Nystatin is fungicidal and also has fungistatic activity, binding to ergosterol in the cell wall, causing leakage.

Theazole class of antifungals, which are widely used, have a very broad spectrum of action, with approximately equal efficacy against both yeast and dermatophytes. These agents are also fungistatic, but, in contrast to nystatin, the azoles work by blocking the synthesis of ergosterol in the cell wall. In addition, oxiconazole—an imidazole agent within the azole class—has been shown to be fungicidal as well as fungistatic.

Allylamines and benzylamines inhibit the synthesis of ergosterol. These agents are fungicidal and highly effective against dermatophyte infections and are fungistatic against Candida.

Like oxiconazole, the hydroxypyridone ciclopirox is both fungicidal and fungistatic, with potent activity against both yeast and dermatophytes. Ciclopirox interferes with active membrane transport and inhibits prostaglandin and leukotriene synthesis.

**NOTES ON INDIVIDUAL AGENTS**

This section highlights some information regarding individual topical antifungal agents that may be helpful in choosing among these agents for specific clinical situations.
As noted above, all of the agents in the azole class are effective against tinea infections, candidiasis, and Malassezia furfur, the cause of tinea ( pityriasis) versicolor. In addition, at least one study has shown that econazole has antibacterial activity. Kates and colleagues compared econazole with vehicle in the treatment of a small group of patients who had bacterial infections of interdigital web spaces, with no evidence of concomitant dermatophytic infection. The infections cleared completely in 88% of patients in the econazole group; none of the patients in the vehicle group had clearance of their infections.

Miconazole also has demonstrated activity against some gram-positive bacterial species. Other agents in the azole class also may have antibacterial activity, but such studies have been reported only on econazole and miconazole.

Oxiconazole is rapidly absorbed into the stratum corneum and, therefore, is effective—and FDA approved—for once-daily use. Efficacy of once-daily dosing was demonstrated by Ellis and colleagues, who compared oxiconazole cream with placebo in both once- and twice-daily regimens in a group of patients with tinea pedis. The cure rates were similar in both active-treatment groups: 80% in the patients who used the drug once a day and 75% who applied oxiconazole twice daily.

More recently, Gupta conducted an overview of the clinical trials that confirmed the efficacy of oxiconazole used once or twice daily, assessed in terms of mycologic cure and clinical response.

In 2000, Crawford and colleagues published a systematic review of the evidence published to date on topical antifungals for tinea infections of the skin and nails of the foot. According to the summary of evidence, activity of the azoles is strongly related to the duration of treatment. For example, the cure rate with clotrimazole after 1 week of therapy was 35%, but after 4 weeks, the cure rate was 70%.

As a class of agents, the allylamines/benzylamines are dramatically more effective as a class of agents for treating dermatophytic infections than for treating yeast infections; for treating the latter, one of the azole antifungals is preferable. One agent in this class, butenafine, is now available as an over-the-counter medication.

Ciclopirox is available in lotion, cream, shampoo, and nail lacquer formulations. The nail lacquer is associated with a cure rate for onychomycosis of only 8% to 12%. In terms of cure, oral therapy with terbinafine yields much higher cure rates, defined as 59% mycologic cure plus new, unaffected nail growth measuring at least 5 mm. However, oral terbinafine—although not contraindicated in pediatric patients—has not been studied to determine the safety or efficacy of this agent for onychomycosis in the pediatric population. Therefore, ciclopirox lacquer may be a better choice for young patients.

Conclusion

Superficial fungal infections caused primarily by Trichophyton species, Microsporum species, Epidermaphyton floccosum, and M. furfur are the most commonly diagnosed skin diseases in the United States. Fortunately, several classes of topical antifungal agents are widely available to safely and effectively treat these infections. Most of these are broad-spectrum antifungals and are active against all of these organisms. Variations exist in demonstrated activity against specific dermatophytes. The choice of individual agents should be based on antifungal activity against the causative organisms (when this is an issue) and on factors that may affect compliance in individual patients.

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References