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Atopic Dermatitis in Children, Part 2: Treatment Options

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Treatment options for children with atopic dermatitis (AD) include environmental modifications, corticosteroids, calcineurin inhibitors, and some less frequently used alternative therapies. Treatment of AD is a multifaceted approach that requires avoidance of specific triggers and irritants, repair and maintenance of the stratum corneum, cessation of the itch-scratch cycle, and reduction of inflammation.

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Part 1 of this series on atopic dermatitis (AD) reviewed the epidemiology, clinical features, and associated complications of AD in children.[1] Part 2 will provide the physician with an overview of the treatment options, including environmental modifications, corticosteroids, calcineurin inhibitors, and some less frequently used alternative therapies. Treatment of AD is a multifaceted approach that requires avoidance of specific triggers and irritants, repair and maintenance of the stratum corneum, cessation of the itch-scratch cycle, and reduction of inflammation.

Environmental Modifications

Treatment begins with extensive counseling regarding appropriate skin care. Patients with AD are advised to avoid soaps and detergents as potential irritants. Patients with AD have been shown to have a decreased threshold of irritant responsiveness and thus should avoid all potential irritants.[2] Soaps and cleansers should be fragrance free. Nonsoap cleansers/syndets can be substituted for soaps. However, avoidance of all soaps is not necessary. A double-blinded placebo-controlled study showed greater clinical improvement and decreased *Staphylococcus aureus* colonization in patients with AD who used an antimicrobial soap containing triclocarban 1.5%.[3]

Clothing detergents should be fragrance free and avoidance of fabric softeners is beneficial as they are nearly always perfumed. Other helpful recommendations include the use of humidifiers to reduce winter dryness, avoidance of occlusive clothing, and short baths or showers with lukewarm water on a daily basis. Excessive heat or moisture exposure can exacerbate skin dryness. Evidence shows that it is not the type of fabric (natural or synthetic) that is associated with skin irritation but rather the texture or roughness of the fabric.[4,5] Therefore, use of washcloths and sponges should be avoided; they are abrasive and can exacerbate illness. A new type of silk fabric, which is silver impregnated and antimicrobial, can be used as a sleep garment to improve AD.[4]

Skin Hydrators/Emollients

Proper skin hydration is necessary to repair and maintain an intact stratum corneum.[6] Emollients should be applied at least daily to prevent disease exacerbations. Application of emollients should be especially encouraged after bathing to seal in moisture. They are the only at-home interventions that have been demonstrated to reduce the need for topical steroids.[7,8] Emollients should be thicker in the winter (eg, petrolatum) and thinner in the summer (eg, creams, lotions).

Anti-inflammatory Agents

Corticosteroids—Oral corticosteroids are not recommended in children with AD. The risks of systemic steroids are thought to outweigh the potential

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benefits in AD. Their use is reserved for severe disease and must be used cautiously and in the smallest dose necessary.[9] Side effects of growth retardation, striae, weight gain, osteoporosis, mood change, cushingoid facies, and aseptic hip necrosis can become a risk with continued use.[10,11]

Topical corticosteroids have been the mainstay of therapy for AD since their release more than 50 years ago. Topical corticosteroids work by reducing inflammation and pruritis[12] and also have been shown to reduce the density of *S aureus*.[13,14]

Topical corticosteroids are rated on a class 1 to class 7 basis, with class 1 being superpotent (eg, clobetasol propionate) and class 7 being least potent (eg, hydrocortisone 0.5%). Fear of side effects from corticosteroids has spread among the general public, specifically atrophy, skin lightening, and development of striae. Some of these fears are realistic and thus class 1 combination corticosteroids and class 2 to class 3 fluorinated corticosteroids (eg, betamethasone valerate and clotrimazole topical) generally are avoided in children because they are more likely to cause atrophy. Atrophy is most likely to occur in covered or occluded areas such as the neck, joints, and groin, as well as on thin-skinned areas such as the face and genitals. Potent topical steroids also can be associated with hypothalamic-pituitary-adrenal (HPA) axis suppression when used in children over a wide body surface area or when fluorinated class 1 and class 2 products are applied under occlusion, such as in the diaper region. More importantly, HPA axis suppression has been seen in infants with widespread application of mometasone furoate, a popular pediatric medicament. Consequently, judicious use and limited application of stronger corticosteroids in infants is recommended. Application of class 1 or fluorinated class 2 products in infants is not advised. Use of class 2 nonfluorinated and class 3 topical corticosteroids over a wide surface area or for extended time (≥3 weeks) is similarly not advised. Use of concurrent emollients helps to limit this risk. In general, application of topical steroids to a large body surface area raises childhood risk for HPA axis suppression and consequent growth limitation and cushingoid features.

While many corticosteroids are available, only a handful have been tested in children. Most steroids can be costly, but fluorinated steroids, such as triamcinolone, may be less expensive. Corticosteroids for pediatric topical use include hydrocortisone (0.5% and 1% cream, lotion, or ointment), which attained over-the-counter status because of limited risk of absorption and systemic side effects. Other topical corticosteroids frequently used with children include mometasone furoate (classes 2–4) approved for children older than 2 years; desonide (classes 5–6), fluocinolone acetonide (class 5), aclometasone (class 5), and prednicarbate (class 4) approved for children older than 1 year; and fluticasone propionate (classes 4–5) approved for children as young as 3 months. A good rule of thumb is that children should experience relief and be near clearance in 2 weeks, though they may not necessarily be clear. If relief has not been achieved within 2 weeks, it is reasonable to increase to a higher potency drug.

A reasonable approach to therapy is to begin treating patients with AD with over-the-counter hydrocortisone (class 7). If this is ineffective, a variety of stronger agents are available. As a rule, pediatricians should avoid prescription of class 1 or class 2 topical corticosteroids. For infants younger than 6 months, use of corticosteroids is best limited to class 4 (mid potency) on the body. In adolescents, class 2 and class 3 (mid potency) products can be used on the body. When mid-potency steroids are used in children, it is advisable to mix them with moisturizers to dilute their strength.

Ointments usually are better tolerated by children with AD. Ointments are more hypoallergenic than creams because they require fewer preservatives to maintain stability. The preservatives in some creams can cause stinging. Gels and solutions are ideal for treatment of the scalp and beard area. Equivalent medicaments will be stronger in ointment form. For example, mometasone furoate ointment 0.1% is a class stronger than mometasone furoate cream 0.1%, consequently with increased risk for side effects.[15]

Topical Calcineurin Inhibitors

A recent addition to the market, topical calcineurin inhibitors expand the ability to treat AD. They have been shown to effectively treat AD in numerous clinical trials.[16-20]

Topical calcineurin inhibitors control phosphorylase activity of the calcium-dependent serine/threonine phosphatase calcineurin and the dephosphorylation of the nuclear factor of activated T-cell protein (NF-AT), a transcription factor necessary for the expression of inflammatory cytokines, including interleukin (IL)–2, IL-4, and IL-5.[21,22]

Topical calcineurin inhibitors do not cause atrophy but work more slowly than topical corticosteroids.[23] Therefore, they are best introduced when topical corticosteroids have failed, with larger body surface areas that would preclude use of corticosteroids, and for eczema with involvement of very sensitive skin, such as the face or neck. In the United States, approval is available for children aged 2 years and older. Indication of use is for patients who have failed topical corticosteroid medications.

The 2 medicaments available are tacrolimus ointments 0.03% and 0.1%, and pimecrolimus cream 1%.[23]

Tacrolimus ointment is approved for moderate to severe AD.[17,18,24-27] Safety data are available for use in children for as long as 3 years' duration and are very promising. Tacrolimus ointment 0.03% is approved for children aged 2 to 15 years and tacrolimus ointment 0.1% for adults. While benefits are not always as rapid as with topical corticosteroids, data have shown that most children experience rapid relief of pruritus within 1 week of twice-daily application. Quality of life also has been shown to improve with use of tacrolimus in children with AD.[17,18,24-27] Reitamo et al[28] published a randomized, double-blinded, controlled trial concluding that tacrolimus ointment is more efficacious than hydrocortisone 1% in children with moderate to severe AD. In head-to-head studies, tacrolimus ointment 0.03% has greater rates of side effects such as pruritus and erythema than pimecrolimus, with similar efficacy at 43 days.[29]

Pimecrolimus is available as an easy-to-apply 1% cream and is approved for mild to moderate AD in nonimmunocompromised patients aged 2 years and older. Safety data are available for children using the medicine for 1 year. Intermittent combined use of corticosteroids for flares is recommended with pimecrolimus. Use of pimecrolimus at the beginning of atopic flares has been shown to reduce the need for topical corticosteroid application and to reduce the overall days of topical corticosteroid use in AD. While pimecrolimus cream 1% has been tested extensively in infants aged 3 to 23 months, the US Food and Drug Administration (FDA) does not recommend use in this age group.[30-34]

Vaccinations should not be altered by application of tacrolimus and pimecrolimus as these medicines do not interfere with immune response to vaccination. Safety of calcineurin inhibitors and sunlight has not been established, and concurrent use of sunscreens is recommended, particularly in summer months.

Recently, the FDA has recommended black-box labeling of topical calcineurin inhibitors (tacrolimus and pimecrolimus), which was enacted in January 2006. The black box states that cancers have been reported with use of calcineurin inhibitors, but no association with the drugs has been made. The black box recommends local intermittent use and avoidance in children younger than 2 years. This black box is a modification of the original FDA Web site–based Public Health Advisory (February 2005), which stated that the topical calcineurin inhibitors have a biological potential to cause skin cancers and lymphomas in humans.[35]

The FDA advisory was predicated on animal trials in which the animals were exposed to extremely high dose medication administered cutaneously or orally and developed dose-dependent cancers.[36,37] The biological potential in humans has not been corroborated in clinical trials, in which the rate of cancer development was not statistically elevated.[35] Isolated case reports of lymphoma in humans on topical calcineurin inhibitors exist; however, the lymphomas were not the kind seen in immunosuppressed individuals. No lymphomas have been reported in pediatric patients treated with tacrolimus and 2 have been reported with topical pimecrolimus. Long-term data in humans, however, will be necessary to fully understand the potential risks. Despite this, on-label use of these medications, including use after failure of topical corticosteroids and avoidance when possible in infants, seems judicious.[35]

Antihistamines

Antihistamines can be given to patients to help them sleep. Studies have shown that they do not improve AD skin lesions, nor do they abort atopic pruritus, as AD pruritus is not histamine based.[38,39] However, antihistamines do help children sleep when pruritus is worst—in the evening.[40] Sedating antihistamines are most effective and dosage should be titrated to maintain nighttime sleep benefit.

Cetirizine, a nonsedating antihistamine, has been shown to have some steroid-sparing effect and may have some long-term benefit in AD in preventing development of asthma.[38,39] Administration for these reasons should be decided on a case-by-case basis.

Antibiotics

Antibiotics are beneficial adjunctive agents in cases of superinfection or excessive crusting and overcolonization. When infection is suspected, bacterial culture should be performed to determine bacterial sensitivity of *S aureus* isolates. Topical mupirocin or oral antibiotics with coverage of *S aureus* (eg, cephalexin, amoxicillin/clavulanate potassium, and dicloxacillin) are good choices, particularly when healing with topical corticosteroids or calcineurin inhibitors has been curtailed by excessive crusting and fissures.[41] Use of antibiotics should be limited to extensive disease or very crusted AD. Treatment usually is more extended (eg, 10–14 days) to allow reduction and suppression of *S aureus* growth in the skin. Methicillin-resistant *S aureus* isolates may respond to good dermatologic care despite therapy with ineffective antibiotics,[42] though recurrence of symptoms would be likely. Excess population-based use of topical mupirocin has been associated with a rise in mupirocin-resistant *S aureus* in selected populations.[43]

Other Therapies

When AD is severe and not altered by topical agents in combination with antibiotics and/or antihistamines, alternative therapies are used.[44-49] Phototherapy with UVB light (300–320 nm), narrowband UVB (311 nm), or UVA-1 have been shown to produce remissions in patients with AD. However, there may be increased lifetime risk for skin cancers, similar to that seen in psoriasis, and relapse often occurs after cessation of treatment.[44-49]

Dust mite avoidance may be beneficial in children with AD who are dust mite sensitive. In particular, dust mite repellant encasings placed over the mattresses and pillows may reduce the incidence of asthma, allergies, and AD in children with a family history of the condition.[50]

Oral immunosuppressants (cyclosporin A and mycofenolate mofetil) work but have the side effects seen in transplant patients. Cyclosporin A is an immunosuppressant that inhibits calcineurin. It has been shown to be effective in decreasing dermatitis and improving quality of life.[51,52] Nevertheless, elevated serum creatinine, hypertension, and renal impairment are potential side effects. Mycofenolate mofetil is a purine biosynthesis inhibitor that also carries the risk of systemic side effects. When patients with severe AD fail topical therapy and UV light therapy, they may have no other choice than to take oral immunosuppressants to improve their quality of life. Interferon-γ also has been reported to be a safe and effective long-term treatment option.[53]

Chinese herbal remedies have been described to help AD by reducing inflammation and suppressing the immune system.[54,55] There is concern, however, that Chinese herbal remedies are hepatotoxic.[56]

Comment

AD is a multifactorial condition that is best treated with a multifactorial approach combining appropriate skin care techniques, topical medicaments, and oral medications that promote normal sleep patterns and reduce bacterial colonization. Using this approach, pediatric patient quality of life can be drastically improved.

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