Bathing and moisturization to control dryness, applications of topical anti-inflammatory agents (including corticosteroids and calcineurin inhibitors [TCIs]) to control flares, minimization of the risk for infection, and relief of pruritus are the cornerstones of effective therapy for atopic dermatitis. Education of parents and patients is crucial to enhance adherence. Strategies for reduced Staphylococcus aureus colonization may help control re-emergence of flares following cessation of antimicrobial treatment for infection; these include dilute bleach baths and minimizing the risk for contamination of topical agents. In severe, refractory cases, more aggressive therapy with systemic immunosuppressants may be considered, but appropriate laboratory testing must be included as part of patient monitoring during treatment. The value of adjuvant therapy with wet wraps to “cool down” particularly erythematous and pruritic flares is becoming increasingly recognized.

Successful treatment of atopic dermatitis (AD) depends on accurate diagnosis and the development of individualized treatment plans. However, achieving these clinical goals does not ensure the best possible treatment outcome unless compliance is also maximized. Too frequently, less-than-optimal response to therapy or treatment failure can be attributed to adherence issues. For example, Krejci-Manwaring and colleagues used microprocessor stealth monitoring of medication use to assess adherence in an AD patient population. These investigators found that overall adherence was only 32%. In another paper from that same study, Feldman and coworkers described how adherence to topical medication regimens markedly increased during the 8-week period surrounding the clinic visit, increasing right before and decreasing a few weeks afterward.
It is important for clinicians to spend time not only educating patients and parents but also exploring the lifestyles of patients’ families to determine which factors might influence medication use and so should be considered in devising a treatment plan. Some areas of discussion should include the time of day when the patient’s bath can be done, how often topical emollients can be applied and when this can be done, and the patient’s and/or caregivers’ preference regarding the type of vehicle in topical medications.

Finally, the concept of written action plans is also critically important. The treatment plan should be discussed, but that information also should be imparted in writing.4

Treatment recommendations in AD are based on the current understanding of pathogenesis—ie, the role of skin barrier dysfunction and of the inflammatory processes that drive the condition.

Bathing and Moisturization

The importance of bathing has long been recognized. Bathing removes some bacteria from the skin, results in some exfoliation, and, importantly, provides hydration. A crucial element of therapy is application after the bath of an appropriate moisturizing agent. Ointments are generally preferred because they reduce transepidermal water loss and, unlike some creams, do not contain preservatives that may sting or burn.

In extremely warm weather, ointments may be too occlusive, and emollient creams are a good alternative in these circumstances. Emollient creams also may be preferred by patients or parents who have strong objections to the greasy feel of ointments. Based on the finding that ceramide tends to be reduced in the skin of patients with AD, some newer emollient agents have been developed that contain this lipid. The amount of ceramide in these products varies. To date, ceramide’s mechanism of action and how much ceramide may be needed to affect barrier function have not been clearly established.

Lotions have a high water content and are appropriate for cases in which dryness is not severe or in very warm weather when excess occlusion from ointments or even emollient creams is a concern.

Several medical devices have become available that are primarily designed to improve the skin barrier. These include N-palmitoylethanolamine, a lipid-based ceramide-dominant cream, and MAS063DP. These have largely been tested in patients with mild to moderate eczema and appear to be superior to vehicle. In more severely affected patients, these may be helpful as adjuvant agents.5

Anti-inflammatory Modalities

Topical corticosteroids remain the mainstay of therapy for bringing AD under control. These are available in a wide variety of strengths, formulations, and vehicles. They range in potency from very-low-strength over-the-counter hydrocortisone to superpotent formulations of various agents (Table 1). Class 2 corticosteroids are the strongest usually used in children; stronger topical formulations are sometimes used in adults and may be used selectively for older children.

When used appropriately, topical corticosteroids are associated with few side effects. The risk for side effects—most commonly, atrophy or striae—increases with excessive use of corticosteroids (in duration of use or in frequency of applications) and when potency is too high, particularly when applied to intertriginous areas or the face. Systemic absorption is a rare possibility with the use of low- or medium-strength corticosteroids, particularly when their application is limited through use of a rotational strategy.

Occasionally, response to a topical corticosteroid may diminish over time in a previous responder, a phenomenon referred to as tachyphylaxis. Reduced or failed response to an agent after initial efficacy suggests the need for a change in the topical regimen, usually to a different corticosteroid of similar potency or to a stronger-potency formulation of the same agent.

However, one of the worst problems associated with topical corticosteroid use is the failure to use the medication, commonly as a result of what has been termed “steroid phobia.” Steroid phobia is the fear on the part of patients’ parents—and even some clinicians—that topical corticosteroids cause significant local and, possibly, systemic side effects. In fact, in one study, steroid phobia accounted for treatment nonadherence in 36% of patients or families.5 This unwarranted fear has an unfortunate adverse impact on the prescription of and/or adherence to use of what are appropriate first-line medications.

Topical calcineurin inhibitors (TCIs)—specifically, tacrolimus ointment and pimecrolimus cream—have been available for the past decade and are indicated as second-line therapy for intermittent use. However, they commonly are used off-label as first-line therapy for facial dermatitis because, unlike corticosteroids, TCIs have not been associated with ocular problems or cutaneous atrophy.

Tacrolimus ointment, 0.03%, and pimecrolimus cream, 1%, are indicated for use in patients 2 years of age or older. In addition, tacrolimus ointment is available in a 0.1% strength, indicated for adults and children more than 15 years of age. The indications for tacrolimus were based on early studies suggesting that the 0.03% and 0.1% strengths were equally safe and effective.6 However, the subsequent widespread clinical experience accumulated with the off-label use of the 0.1% formulation of tacrolimus in children shows that it is actually more effective than the 0.03% formulation for pediatric patients. In addition, evidence supports the safe and effective use of the 0.03% formulation of tacrolimus ointment7 and pimecrolimus in children less than 2 years of age, including infants.8,9

In 2005, a committee convened by the US Food and Drug Administration (FDA) discussed the possibility of adding a black box warning in the prescribing information for TCIs. The discussions centered on the two areas of concern. The first was that high-dose oral calcineurin inhibitors, given as immunosuppressants in patients who received organ transplants, was associated in a minority of these patients with post-transplant lymphoproliferative disorder, in addition to their increased potential for causing ultraviolet-light–induced nonmelanoma skin cancer. The second area of concern was that administration
of very high doses of oral calcineurin inhibitors was associated with lymphoma in some animal studies.

The FDA committee recommended inclusion of a black box warning based on the theoretical possibility of malignancy, which was instituted in 2006 and remains in effect to date. However, in more than a decade following their introduction, no evidence has emerged to indicate that TCIs increase the risk for these problems in individuals who use them for AD. In fact, one case-controlled study of 5,000 adults with dermatitis showed that 26% of subjects who had been exposed to TCIs had a decreased risk for nonmelanoma skin cancer, with the odds ratio for this association decreasing as the number of tubes used or the potency of the TCI increased.10

Arellano and colleagues11 examined the risk of lymphoma in AD in two studies. A case-controlled study of more than 2,700 cases from the UK database of lymphoma among 3.5 million persons and about 11,000 matched controls demonstrated an increased risk of lymphoma in patients with AD in general, particularly in more severe cases. A correlation was shown between lymphoma and high-potency topical corticosteroids, but not TCIs, in the AD population. The other study by these investigators was a nested case-controlled study of close to 300,000 patients with AD, approximately 59% of them children.12 Three hundred cases of lymphoma were identified and, again, were correlated with disease severity but not with the use of TCIs.

Moreover, no signal of concern has emerged in data relating specifically to children. By 2011, an ongoing 10-year safety study of tacrolimus had enrolled more than 6,000 children, and—based on Surveillance, Epidemiology, and End Results (SEER) data—no increased incidence of lymphoma or nonmelanoma skin cancer had been noted. Serious adverse events—primarily asthma—were reported in less than 5% of patients.13

Rotational and Intermittent Therapy Strategies

The concept of rotation therapy emerged with the increased understanding of and attention focused on the skin barrier in AD. Studies of the effects on skin barrier function of topical
corticosteroids and TCIs have demonstrated that corticosteroids compromise skin barrier function with long-term therapy and that this compromise actually may happen fairly quickly—within as little as 2 to 3 days with some of the higher-potency agents. In contrast, repair of some of the corticosteroid-induced barrier has been seen with TCIs.

Taking advantage of these mechanisms, rotational therapy involves the initial use of a medium-strength topical corticosteroid for AD flares, then switching to a TCI (rather than a lower-strength corticosteroid) when the flare is under control. To minimize long-term, chronic application of corticosteroids—and the risk for chronic impairment of barrier function—intermittent therapy should be considered as maintenance treatment. Hanifin and colleagues tested this strategy with twice-weekly applications of fluticasone cream as maintenance and found it to be effective. This concept of “dialing down” was subsequently tested using tacrolimus ointment to decrease corticosteroid use for maintenance. Several studies have demonstrated that, once a flare is under control with corticosteroids and the skin in that area is clear or almost clear, the application of tacrolimus two to three times weekly provides an effective means of extending the corticosteroid-free periods between recurrent flares.

A maintenance schedule of twice-weekly application of TCIs to clear or almost-clear areas is currently indicated in Europe.

Preventing and Managing Infections

Infection in patients with AD, heralded by crusting or pus-tules, is treated with systemic antibiotics; topical antibiotics have been tried but have not proved to be effective. Interestingly, decades of experience with certain systemic agents—for example, cephalaxin—has shown that antimicrobial therapy often results in dramatic improvement of inflammation as well as control of an infection. To date, however, no good clinical trial has been published that supports this clinical observation.

It is not uncommon for patients to experience an AD flare within a few days to a few weeks following completion of the oral antibiotic regimen. The timing of this flare tends to correlate with the severity of a patient’s disease and reinfection. Presumably, the flare and reinfection tendency relates to Staphylococcus aureus overgrowth, and several groups currently are investigating ways to prolong improvement following oral antibiotic therapy.

One relatively new technique that has become the standard of care in the United States for infection-prone patients with AD is the dilute bleach bath—that is, adding sodium hypochlorite (chlorine bleach) to bath water. Huang and colleagues conducted a study of 31 children with moderate to severe AD and skin infections, in which decreasing S. aureus colonization in the nose and on the skin was associated with a decrease in severity of AD. In this study, nose and skin cultures were obtained prior to initiation of oral cephalexin treatment. Patients were then randomized to receive either bleach in their bath water plus a monthly course of intranasal mupirocin or no bleach in their bath water and a placebo for intranasal administration. Family members of the bleach bath group also received intranasal mupirocin; family members of the no bleach group were given intranasal placebo.

With twice-weekly bathing, both eczema severity and the affected body surface area (BSA) had dramatically decreased in the bleach bath/intranasal mupirocin group, reaching statistical significance by 1 month ($p = 0.02$ for Eczema Area and Severity Index [EASI]; $p = 0.05$ for BSA) and even greater significance by the end of the study at 3 months ($p = 0.004$ for both EASI and BSA). A post hoc analysis showed that these differences were evident only on the limbs and trunk—the areas of the body submerged in the bath; no differences were noted between the two groups in AD sites on the head and neck, which were not submerged. Cultures performed throughout the study demonstrated the persistence of S. aureus colonization; thus, the number of organism was suppressed, but S. aureus was not eliminated.

Dilute bleach baths must be continued as a maintenance treatment for S. aureus overgrowth to remain suppressed. The current recommendation for the concentration of bleach in the bath is 0.005%. The typical concentration of sodium hypochlorite in common household bleach (used in laundry, for example) is 6%, so ¼ cup of bleach added to a half-filled, standard, 40-gallon bathtub (or ½ cup added to a full bathtub) will yield the proper concentration. If a baby bathing basin is used, the proper concentration can be achieved by adding 3 cc of household bleach to each gallon of water.

Other steps should be considered to minimize S. aureus exposure in patients with AD, particularly in those who have already experienced one or more infections. One possible source of S. aureus contamination that has been discovered in recent years is unpreserved topical agents (prescription and nonprescription) used in AD. In one study, Carr and colleagues cultured bacteria from the rims, nozzles, and containers of ointments, emollients, and topical corticosteroid medications. About half of the containers were contaminated by S. aureus, and of these, S. aureus was cultured in half. Keeping in mind the ubiquitous nature of S. aureus, clinicians should consider advising parents to keep moisturizers and topical medications in the refrigerator (warming them by floating them in the bathtub prior to after-bath application). Parents also should be instructed to use a tongue blade or a clean spoon to remove medications and moisturizers from their containers, thereby avoiding hand contamination of the remaining product.

Furthermore, in cases in which infections are recurrent, it may be helpful to have family members use mupirocin intranasally and also to use mupirocin ointment on the hands. In one study of bacterial cultures from skin and nares, 65% of parents also showed S. aureus colonization, and in 84% of these isolates, the S. aureus characteristics were shared with those of their children with AD. In the future, other measures such as the use of alternative antiseptic products (cur-
recently in development or being studied) or antibacterial clothing may help reduce recurrent infections in susceptible patients with AD.

**Refractory AD**

In patients who do not respond as expected to appropriate management and in whom tachyphylaxis has been ruled out by changing topical medications, the possibility of an incorrect diagnosis must be considered. Many conditions mimic AD and range from genetic disorders such as Netherton syndrome, hyper–immunoglobulin E syndrome, and Wiskott-Aldrich syndrome to conditions like allergic contact dermatitis, secondarily eczematized scabies, and tinea incognito.

In addition, studies have shown that contact dermatitis can coexist with AD.25 Beattie and colleagues26 showed that 6% to 22% of patients with AD had a positive patch test beyond nickel, and half of them were sensitive to agents in their emollient. Thus, it is important to be mindful that additives used in emollients, skin cleansers, and even topical corticosteroids can be contact sensitizers.

After considering and ruling out these alternative explanations for failure to respond adequately, more aggressive approaches can be considered. One of these is hospitalization, during which patients can receive careful monitoring and intensive attention, including ready access to consultants. Hospitalization has the added advantage of providing respite for the family, as well as a focused opportunity for them to receive further education about the proper use of medications. Of course, hospitalization itself presents certain risks, including that of exposure to bacterial infection, so the duration of the stay should be minimized.

Systemic intervention is an option in some patients, and the patient's and family's quality of life should be included as factors when considering such a decision. The process must include a discussion with the family concerning the risks for infection and neoplasia, particularly lymphoma.

No large comparative trials have been published, and no detailed treatment guidelines currently exist on the use of systemic immunosuppressants for AD in children. Some case series have been published.27-32 These studies all show the potential efficacy and limited toxicity of these immunosuppressants when used for limited periods and with careful monitoring (as described below).

In general, topical anti-inflammatories should be continued during initiation of systemic immunosuppressant therapy, and these topicals subsequently phased out, if possible. If topical therapy is continued, a rotational strategy should be considered. Side effects from appropriately used topical agents are unusual, even with concomitant use of systemic immunosuppressants.

Nonsteroidal immunosuppressants are preferred because of the potential side effects associated with the use of systemic corticosteroids. In addition, rebound flare of AD is a common problem in children when systemic corticosteroids are discontinued.

More commonly, cyclosporine, azathioprine, mycophenolate mofetil, and methotrexate are used. Among these immunosuppressants, cyclosporine has the most rapid onset of action. A meta-analysis that included 15 studies showed that cyclosporine administration was associated with a decrease in disease severity by 55% at 6 to 8 weeks.27 In addition, open-label studies have been done in children, specifically, using 5 mg/kg/day, adjusted as needed for therapeutic effect. This regimen has yielded reductions in severity of scores ranging from 50% to 60% after 6 to 8 weeks of treatment.28,29 Continuous administration of cyclosporine, tapered to the lowest therapeutic level, seems to yield approximately the same clinical results as administration of intermittent 12-week courses of therapy.30 The effective dose should be maintained for a few months and then tapered gradually, with exposure to cyclosporine limited to 1 year.

Azathioprine has received greater attention recently30,31 and is the treatment of choice in the United Kingdom. In a study of 48 children, Murphy and Atherton32 found an excellent response in about 60% of children with severe AD at 3 months. Azathioprine has a delayed onset of efficacy of 4 to 6 weeks, so some clinicians begin concurrent treatment with azathioprine and a corticosteroid, tapering off the corticosteroid starting 1 month later. In general, the optimum dosage is 2.5 to 3.5 mg/kg/day of azathioprine; however, if an intermediate level of the erythrocyte thio- purine methyltransferase (TPMT) enzyme is obtained (see the discussion of monitoring, below), that dosage can be adjusted downward to 1 mg/kg/day. An effective dose should be maintained for about 3 months, then tapered gradually; azathioprine can be used for 2 years before transitioning to an alternative therapy.

Another option is mycophenolate mofetil, which is among the least toxic (although costlier) systemic immunosuppressants for AD. As with azathioprine, mycophenolate mofetil's onset of efficacy is delayed for 4 to 8 weeks. The maximal effect is seen at 8 to 12 weeks after initiation, so, here again, concurrent administration of corticosteroid at the start of therapy, followed by tapering and then discontinuation, is advisable. In a study by Heller et al,33 58% of patients showed greater than 90% improvement, and 93% of patients showed greater than 60% improvement. In children, a dosage of 40 to 50 mg/kg/day (or 600 to 1,200 mg/m2) is the usual dosage. For adolescents, a dosage range of 30 to 40 mg/kg/day will yield a maximum level of 3 g/day. The use of mycophenolate mofetil should be limited to 2 years.

Finally, methotrexate has been found to be helpful, particularly once a flare has subsided. In fact, methotrexate probably is most suitable for maintenance in severe AD. For this use, the dosage is 0.5 to 0.6 mg/kg/week, with a maximum of 20 mg. This can be administered in a single dose each week, although some clinicians have found that efficacy is greater if the dosage is divided over several consecutive days. Concomitant administration of folic acid is important during methotrexate therapy. No studies of methotrexate have been done in children with AD. In a study of adults, Weatherhead et al34 demonstrated that
methotrexate resulted in a decrease in severity of 52% from baseline over a 24-week period.

Clinical and laboratory monitoring is crucial during treatment with systemic immunosuppressants (Table 2). Among the four agents discussed here, cyclosporine is associated with the greatest number of potential side effects. Neoplasia is a potential long-term risk. Shorter-term, increased risks for infection, renal and hepatic toxicity, and hypertrichosis are associated with cyclosporine. During treatment, blood pressure should be monitored weekly for 1 month, then monthly thereafter. Baseline laboratory tests should include complete blood count (CBC), liver function tests, and blood-urea-nitrogen and creatinine levels; these tests should be repeated monthly for at least the first few months, then every other month thereafter.

With the use of azathioprine, a baseline level of erythrocyte TPMT should be obtained; inadequate levels of this enzyme are associated with the greatest risk for myelosuppression. Baseline CBC and liver function tests also are important. These studies should be repeated every 2 weeks for 1 month, then monthly for 2 months, and every 2 months thereafter for the duration of treatment.

For mycophenolate mofetil and methotrexate therapy, monitoring should include baseline CBC and liver function tests, repeated monthly for 2 months, then every 3 months for the duration of treatment.

An alternative to systemic immunosuppressive treatment is phototherapy, preferably with narrowband ultraviolet B (UVB) light. Clayton and colleagues35 presented a retrospective review of 50 children with severe AD who were treated with at least 10 exposures to narrowband UVB. Complete clearance was seen in 40% of patients, with good improvement in 23% and moderate improvement in 26%; the median length of remission was 3 months.

There are several disadvantages to using narrowband UVB in children. First, it requires cooperation by the child, either alone or with a parent in the phototherapy booth. Second, the time commitment required for treatments is often difficult to secure, conflicting with parents’ work schedules and children’s school and recreational activities. Third, the potential risks for skin cancer and premature aging are unknown at this time.

**Adjuvant Therapy**

Wet wraps are a traditional method for decreasing inflammation and pruritus and increasing comfort, particularly during an AD flare. Some centers, such as the Mayo Clinic, have used

<table>
<thead>
<tr>
<th>Test</th>
<th>Azathioprine</th>
<th>Cyclosporine</th>
<th>Methotrexate</th>
<th>Mycophenolate mofetil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>—</td>
<td>Monitor weekly for 1 month, then monthly thereafter</td>
<td>Baseline, then monthly for the first few months, then every other month for duration of therapy</td>
<td>Baseline, then monthly for 2 months, then every 3 months for duration of therapy</td>
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<tr>
<td>CBC</td>
<td>Baseline, then every 2 weeks for 1 month, then monthly for 2 months, then every 2 months for duration of therapy</td>
<td>Baseline, then monthly for the first few months, then every other month for duration of therapy</td>
<td>Baseline, then monthly for 2 months, then every 3 months for duration of therapy</td>
<td>Baseline, then monthly for 2 months, then every 3 months for duration of therapy</td>
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<tr>
<td>Liver function tests</td>
<td>Baseline, then every 2 weeks for 1 month, then monthly for 2 months, then every 2 months for duration of therapy</td>
<td>Baseline, then monthly for the first few months, then every other month for duration of therapy</td>
<td>Baseline, then monthly for 2 months, then every 3 months for duration of therapy</td>
<td>Baseline, then monthly for 2 months, then every 3 months for duration of therapy</td>
</tr>
<tr>
<td>BUN level</td>
<td>—</td>
<td>Baseline, then monthly for the first few months, then every other month for duration of therapy</td>
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<tr>
<td>Creatinine level</td>
<td>—</td>
<td>Baseline, then monthly for the first few months, then every other month for duration of therapy</td>
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<tr>
<td>Erythrocyte TPMT enzyme</td>
<td>Baseline, then every 2 weeks for 1 month, then monthly for 2 months, then every 2 months for duration of therapy</td>
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BUN, blood-urea-nitrogen; CBC, complete blood count; TPMT, erythrocyte thiopurine methyltransferase.
inpatient wet-wrap therapy for rapid control of pediatric AD. The method has gained renewed and more widespread interest in recent years, and several authors have provided evidence of efficacy and guidelines for use in AD.

This technique is simple enough to use at home. Following a bath and application of medications and moisturizers, the affected areas are wrapped in wet gauze and topped by a dry layer. If the AD is widespread, it is more convenient (and cost-effective) to dress the child in wet pajamas, followed by warmed, dry towels or blankets. Wet wrapping used at night can decrease pruritus and help children sleep. This technique usually is more successful in infants and toddlers; older children may refuse to leave the wet wraps in place or may refuse to allow the treatment at all. One needs to keep in mind that when using a topical corticosteroid, wrapping will increase the potential absorption.

Antihistamines are not particularly useful for decreasing pruritus associated with AD, but can be very helpful to promote sleep when used at sedating dosages—for example, hydroxyzine given at 1 mg/kg/day.

**Conclusion**

A number of effective and safe agents are available to manage AD flares and extend periods of remission between flares. However, no single regimen will work for all patients with AD. Treatment strategies must be individualized and modified over time as patient needs require and, in the case of children, as caregiver adherence permits. Sufficient time must be spent educating patients and parents about the risks and benefits of therapy as well as allaying unfounded fears about medication side effects, particularly regarding topical corticosteroids.

**References**