Management of Difficult-to-Treat Atopic Dermatitis

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Atopic dermatitis is a complex disorder caused by the interplay between multiple genetic and environmental factors. Particularly in patients with severe disease, the effect is not just an itchy rash but also the secondary effects on the psychological well-being of the patient and their carers, particularly disturbed sleep. The aim of this review is to provide health care professionals with a holistic approach to the management of difficult-to-treat atopic dermatitis, defined as atopic dermatitis seemingly unresponsive to simple moisturizers and mild potency (classes VI and VII) topical corticosteroids. The critical importance of education and advice is emphasized, as is the seminal role of secondary bacterial infection and polyclonal T-cell activation in causing acute flares in patients with severe, generalized disease. In atypical cases or those that do not respond to treatment, alternative diagnoses should be considered. © 2012 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;1:142-51)

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SIZE AND EXTENT OF THE PROBLEM

Recent population surveys from both sides of the Atlantic suggest that the prevalence of atopic dermatitis (AD) is approximately 17% to 18%.[1,2] The proportion of patients having a physician diagnosis of AD is however only 15% to 37% of the total. Of those who see a primary care physician, AD severity scoring indicates that >70% of patients have mild disease that is dealt with in primary care, but approximately 20% having moderate and 2% severe AD, often requiring referral to specialists such as general pediatricians, dermatologists, or allergists.[3] Between 1994 and 2004 there were 7.4 million visits of children younger than 18 years to US physicians for AD.[4] Topical corticosteroids were prescribed in 25% to 34% and calcineurin inhibitors in 23% of visits. The national estimated cost of treatment for this condition is as high as US $3.8 billion per year.[5] For the purposes of this review, we define *difficult-to-treat AD* as AD apparently unresponsive to simple moisturizers and mild potency (classes VI and VII) topical corticosteroids, often requiring referral to a specialist.

REASONS FOR TREATMENT FAILURE

Incorrect diagnosis

An uncommon but important cause of treatment failure is incorrect diagnosis. Diagnosis of AD is based on Hanifin and Rajka's Clinical Diagnostic Criteria (3 of 4 major criteria: pruritis, typical appearance and distribution, chronicity, personal or family history of atopy, as well as at least 3 minor criteria)[6] or a modification developed more recently by the British Association of Dermatologists[7] and the American Academy of Dermatology Consensus Conference on Pediatric Atopic Dermatitis.[8]

Medical conditions that may be confused with AD are listed in Table I. These conditions include other primary skin, immunodeficiency, and metabolic diseases, as well as skin infection, malignancy, and drug reactions. Rashes that are not typical of AD because of their distribution, lack of pruritus, or poor response to appropriate application of topical ointments; patients with a past medical history of medical problems such as systemic infections or gastrointestinal symptoms; and patients with an unusual family history should alert the physician to alternative diagnoses.

Lack of education and compliance

The reason for treatment failure in more than one-half of patients referred to specialist centers is that the treatment is not being administered.[9-11] Reasons for inadequate administration are summarized in Table II. Doctors often have insufficient time to educate patients and their caregivers about the correct application of ointments and creams,[12] and this adversely affects compliance.[13] In one published survey, only 5% of 51 parents attending a specialist pediatric dermatology clinic had

Abbreviations used
AD- Atopic dermatitis
APT- Atopy patch test
SIT- Specific immunotherapy

received/recalled receiving any explanation of the causes of AD or a demonstration as to how to apply topical treatments.[14] Written action plans should be considered because they will help to reinforce the information provided at the consultation.[15] Many countries have patient support groups that provide useful supplementary literature, for example, in the United States, the National Eczema Association, in the United Kingdom, National Eczema Society, and in Canada, the Eczema Society of Canada.

Hypersensitivity reactions to treatment

Vehicles or active ingredients in topical medication may directly inflame the skin, either because of chemical irritation or immune hypersensitivity. For example, urea-containing emollients may cause stinging, and tacrolimus ointment and pimecrolimus cream may cause transient burning and erythema, lasting 3 to 5 days. Thiols, primary amines, alkenes, and alkyl halides have the capacity to form covalent bonds with surface-bound proteins on keratinocyte membranes, resulting in delayed hypersensitivity responses.[16] Examples are propylene glycol, formaldehyde, and sorbitan sesquioleate that are used as vehicles in emollients,[17] chemical stabilizers (eg, ethylenediamine) incorporated into topical medication,[18] and even some halogenated corticosteroids (hydrocortisone-17-butyrate and betamethasone-17-valerate).[19]

Patients who report that the ointment or more often cream makes their AD flare should be considered for a period of avoidance and patch testing. Patch testing detects delayed cellular hypersensitivity to allergens and is typically performed by dermatology and allergy specialists with the use of international guidelines to a battery of 50 or more different chemicals. The procedure requires a number of visits to specialist units over a period of 4 to 5 days for application, removal, and then interpretation of the results. A recent North American multicenter review of 427 adults with contact dermatitis showed that of standardized patch testing allergens, the 5 most common positives were nickel sulfate, fragrance mix I, p-phenylenediamine, thimerosal, and cobalt chloride.[20]

Secondary skin infections

Most patients with AD carry *Staphylococcus aureus* on their skin.[21,22] Skin infections, particularly with staphylococcus-expressing exotoxins are known to exacerbate AD.[23-26] Group A

TABLE I. Brief guide and distinguishing features of diseases that may be mistaken for AD

Disease	Clinical characteristics	Diagnosis/laboratory tests
Primary skin conditions		
Netherton syndrome	Erythroderma, ichthyosis, poor hair growth (trichorrhexis invaginata/nodosa)	Microscopic examination of hair (bamboo stalk appearance), absent LEKTI staining on immunohistology, *SPINK5* gene mutation screening
Keratosis pilaris	Papular rash "chicken skin" on face and outer aspects of the upper arms and thighs	Clinical diagnosis
Psoriasis	Classically raised red plaques with silvery scales	Clinical diagnosis
Primary immunodeficiency diseases		
Severe combined immunodeficiency, especially Omenn variant	Particularly in infant >6 months; recurrent or persistent chest infection, diarrhea, candidiasis, failure to thrive, erythroderma	Absolute lymphocyte count $<2.8 \times 10^9$/L in infants younger than 3 mo, lymphocyte subsets, gene mutation screening
Wiskott-Aldrich syndrome	Male; infections, petechiae, epistaxis, bloody diarrhea or history of bleeding	Thrombocytopenia with low mean platelet volume, *WASP* gene mutation
Primary metabolic conditions		
Acrodermatitis enteropathica	Infants; periorofacial and acral dermatitis, alopecia, diarrhea, failure to thrive	Plasma zinc concentration, *SLC39A4* gene mutation screening
Other		
Skin infections, including impetigo and dermatophytosis		
Bacterial	Oozing, crusting painful lesions	Skin swabs
Fungal	Classically itchy, red, sometimes scaly raised rings surrounding a paler center; associated hair loss	Skin scraping for fungal hyphae
Seborrheic dermatitis	Scaly, flaky, itchy red skin on scalp/body	Clinical diagnosis
Scabies	Itchy with superficial burrows on hands, feet, arms, legs, perineum	Clinical diagnosis
Drug reactions, contact dermatitis to topical creams and ointments	Polymorphic rashes vary from urticaria, maculopapular, or erythroderma to blistering	Patch tests for contact dermatitis, improvement after drug withdrawal
Malignancies		
Cutaneous T-cell lymphoma	Adults; raised plaques, nodules, and ulcers	Biopsy
Letterer-Siwe disease	Infants, young children; seborrheic rash, lymphadenopathy, hepatosplenomegaly	Biopsy

LEKTI, Lympho-epithelial Kazal-type inhibitor.

TABLE II. Reasons for noncompliance with medication

Medication unavailable
• Patient runs out of medication and does not go to the physician for further scripts.
• Physician unwilling to prescribe adequate amounts of medication because of concerns about toxicity or cost.
Medication is available but not used
• Patient/parents are unaware of the correct frequency and the type of medication that should be applied for effective management of AD.
• Patient/parents lack motivation; AD felt not to be so bad that treatment is required.
• Patient/parents have poor time management skills.
• Application is left to children who are too young to apply the medication effectively.
• Patient's/parent's perception is that treatment does not work.
• Patient's/parent's perception is that treatment has unacceptable side effects.
• Patient's/parents perception is that treatment is cosmetically unacceptable (eg, shiny ointments to face of teenagers).
• Medication makes AD worse.
• Medication is painful to apply.

or C streptococci are less common triggers.[27] Clinical features that suggest secondary bacterial skin infection are (1) painful, oozing, or crusting lesions; (2) an asymmetrical distribution; and (3) extensive disease. Methicillin-resistance *S aureus* is a growing problem in patients with AD.[28,29]

Other microbes can also cause flares. In particular, the development of monomorphic vesicles suggests secondary infection with the herpes simplex virus. This is one of the true emergencies in clinical dermatology, requiring prompt systemic antiviral therapy.[30] *Malassezia* species are common skin commensals and in 75% of adults. It is found particularly in the head and neck area, leading to tinea vericolor. In infants, it is more likely to be associated with seborrheic dermatitis than with AD.[31,32]

Food and aeroallergens

Food-induced flares occur in approximately one-third of infants and young children and in 5% to 10% of older children with moderate to severe AD but are uncommon in adults.[33] The diagnosis of food-induced flares is not as straightforward as the diagnosis of immediate-type allergic reactions to foods (urticaria and angioedema). Unlike immediate-type hypersensitivity reactions, food-induced flares in AD may occur, even when the food-specific IgE is negative. Thus, although allergen-specific IgE and skin prick tests may be helpful in supporting the clinical diagnosis of immediate hypersensitivity reactions, they may be falsely negative in patients with food-related AD flares.[34] False-positive specific IgE tests are also common because patients with AD often have high concentrations of total serum IgE.

Patch testing is theoretically more relevant because it measures delayed rather than immediate hypersensitivity reactions.[35] The European Task Force on Atopic Dermatitis has developed a standardized technique for the atopy patch test (APT).[36,37] APT is an epicutaneous patch test that uses allergens known to elicit IgE-mediated reactions such as cow's milk protein, house dust mite, and pollens rather than antigens that classically only cause a delayed contact dermatitis. A study that investigated patch testing in 437 children with AD and possible food allergy concluded that APT added little to predicting the likelihood of food-exacerbated eczema.[38] A review on the topic concluded that current evidence was insufficient to recommend APT in routine practice.[39]

The diagnosis of food-induced flares of AD thus rests with a 4-week period of dietary exclusion of the specific food to confirm that the AD improves. In patients in whom the clinical history suggests an immediate hypersensitivity to the food, a formal physician-observed food challenge should then be performed at a medical facility to confirm that the food does induce an allergic reaction.[40] When the clinical history indicates that a flare of AD occurs over hours to days after eating the food, reintroduction of the food can be undertaken at home to confirm whether it does indeed lead to an exacerbation of the AD. Particularly in infants and young children, exclusion of specific foods supervised by dieticians may reveal food triggers that are not apparent from the clinical history or rule out foods that caregivers believe cause the AD to flare.

A Cochrane review of 9 randomized controlled trials of food exclusion concluded that there is no benefit of milk and egg exclusion, few food diets, or elemental diets in unselected patients with AD.[41] However in selected cases, foods allergens may be an important trigger. For instance, evidence suggests that egg avoidance in patients with a history of egg allergy does reduce AD severity.[41,42] Patients with a clear history of eczema flares after eating specific foods are most likely to benefit from a trial of avoidance. In infants and young children with AD who do not respond to emollients and mild potency corticosteroids, a trial off cow's milk formula might be undertaken with the help of a dietician. It should be made clear to the patient that the trial of food avoidance is initially for 4 weeks after which time the effect of this intervention is to be reviewed. Many children will outgrow food-related flares; therefore, in patients in whom food is a trigger, reevaluation is required at 6- to 12-month intervals.

House dust mite and other aeroallergens are often implicated as triggers of AD.[43] Standard skin prick tests and allergen-specific IgE measurements cannot be used to assess delayed hypersensitivity reactions to these or other allergens. Studies are conflicting as to whether standard measures of dust mite avoidance reduce AD severity.[44-47] Measures for dust mite control should be considered, especially in patients with concurrent asthma or perennial rhinitis triggered by dust mites. In patients whose AD consistently flares when they are around animals, contact with these animals should be avoided.

Psychosocial factors

The psychosocial effect of AD on the child and the parents is well recognized, particularly in relation to sleep disturbances at night. Sleep deprivation can impair daytime functioning of both patients and their children, and in parents it is associated with an increased level of anxiety and depression.[48,49] In a study of 284 adults with AD, stress and emotional state were reported as a commonly reported trigger,[50] and emotional response was just as, if not more, likely to be of primary concern in patients and their caregivers as the severity of the AD itself. Number and duration of sleep disturbances during the night provide a simple measure of the effect the AD is having on quality of life. Social factors in the home and school/work environment (eg, family disharmony, bullying, and other significant life events) should be enquired about in the clinical history because they may affect the severity of the disease.[51]

Adults compared with children

Although 85% of AD presents by 5 years old and 70% remits by adolescence, AD that persists into adulthood can be difficult to manage. AD starts in adulthood in 2% to 8% of cases, and in these patients alternative causes should be considered (Table I). Food-related flares are common in infants and young children, but they are relatively rare in adults. In adults, contact irritant and allergic dermatitis after exposure to perfumes, deodorants, washing powder, gloves, and jewelry at home or to chemicals and dusts from occupational exposure in the workplace need to be considered, in which case avoidance will be an important part of the patient's management.[52] Fungal infection with *Malassezia* is more common, particularly when AD affects the head and neck. If skin scrapings are positive, topical antifungal therapy is indicated.[53] Psychological factors that affect both home and work life should also be considered because studies suggest that behavioral therapy may be beneficial.[54]

THERAPEUTIC OPTIONS

The management of difficult-to-control AD should focus on the questions listed in Table III. A thorough history of the patients' symptoms, medication use, and understanding of the disease; physical examination; and identification of possible trigger factors as detailed earlier should be obtained. Patients with refractory AD should be managed by specialists (pediatricians, dermatologists, or allergists) with the necessary expertise and support staff (nursing and dietary). Hospitalization should be considered for patients who are resistant to outpatient therapy. In many cases, intensive education and adherence to therapy, as well as treatment of secondary infections and removal of allergens or stressors, result in sustained improvement of AD. If the diagnosis is in doubt because of atypical clinical features or poor response to treatment, a second opinion should be sought. Skin biopsy is not indicated for patients with AD unless alternative diagnoses are being considered for which histology or microbiology may provide additional useful information.

TABLE III. Approach to difficult-to-treat AD

I. Is the diagnosis of AD correct?
II. Does the patient have a good understanding of AD? • Chronic disease/exacerbations and remissions • No cure • Appropriate general measures
III. Is current treatment optimum? • Adherence • Under treatment: hydration, inadequate prescription of steroid, cost constraints • Topical therapy not applied properly
IV. Are there any trigger factors? • Infection: bacterial (eg, *Staphylococcus aureus*), viral (eg, herpes simplex), fungal (eg, tinea corporis) • Allergens: foods, aeroallergens • Irritants: detergents, soaps, chemicals, preservatives, clothing, heat
V. Are there any psychosocial disturbances? • Emotional stress: anger, frustration, anxiety, family dysfunction, bullying

Difficult-to-treat AD is defined as AD that does not respond to simple moisturizers and mild-potency (classes VI and VII) topical corticosteroids and typically requires referral to specialists.

Patient education and compliance

An appreciation of the chronic nature of AD, exacerbating factors, and appropriate treatment options is important for both patients and family members. A systematic review of randomized controlled trials that involved educational intervention in adolescent and adult patients reported significant benefits,[55] including improved self-care, increased knowledge of treatments, and improved disease control.[56-59] Educational interventions should be delivered by suitably trained personnel and need regular reinforcement. Clinicians need to provide both general information and detailed skin care recommendations. Clear verbal and written outlines of the skin care plan are essential for a good outcome. Availability of patient-oriented support organizations and updates on progress in AD research are also beneficial.

Moisturizers

With the wider recognition of AD as primarily a disease of skin barrier function,[60,61] moisturizers remain an important therapeutic intervention to reduce xerosis. They are steroid-sparing and help to restore and maintain skin hydration.[62-64] Moisturizers have a number of properties, including (1) occlusive (lipids; eg, petrolatum/liquid paraffin) to prevent water loss and in this regard ointments are better than creams; (2) humectant (eg, glycerin, 5% to 10% urea, lactic acid) to attract water into the stratum corneum; and (3) emollient (eg, cholesterol, fatty acids) to smooth skin by filling spaces between skin flakes with droplets of oil. Ceramides are a main lipid constituent in the skin and play an essential role in barrier function and water retention. The skin of patients with AD has a reduced total ceramide content. Ceramide-dominant emulsions restore the normal balance of the lipids and have been shown to reduce transcutaneous water loss, but their advantage over other moisturizers is yet to be determined.[65]

In terms of potential side effects, occlusives can cause a greasy texture, folliculitis, and sweat retention and may not be tolerated by adolescents and adults or by people living in hot climates. Humectants used for long periods may lead to irritation and long-term drying. Preservatives and fragrances, particularly in creams, can cause contact dermatitis. To promote adherence, families and patients should be given a choice of moisturizers. For young children with severe AD, application of moisturizers frequently, such as with each diaper change, may be useful.

Topical corticosteroids

Topical corticosteroids remain the mainstay of treatment in AD. The choice of agent varies according to the location and severity of the skin lesions. As a general rule and particularly in children, the lowest potency corticosteroid that is effective should be used. Corticosteroids should be used sparingly, and a "fingertip unit" is sufficient to cover twice the area of the handprint.[66] Side effects are infrequent with low-potency topical steroids even when applied over long periods. Skin atrophy is the most common side effect with higher potency preparations. Hypopigmentation, secondary infection, acne, and striae (which are permanent) may also occur. Local side effects are most likely to occur on the face, neck, and in the intertriginous areas; thus, only a low-potency corticosteroid should be used on these areas. If the response to mild-potency corticosteroids is suboptimal on these areas, then calcineurin antagonists should be considered in preference to more-potent steroids. Potent and very potent

topical corticosteroids may be necessary for refractory AD. They should be used for short periods, and very potent steroids should be avoided in children.[67] Particularly in infants and young children with refractory AD, alternative diagnoses and food- and infection-related triggers should be considered.

The vehicle through which the active steroid is delivered plays an important role in absorption and can enhance its efficacy. Generally, ointments are more effective than creams, because the occlusive effect results in better penetration. Ointments also contain fewer preservatives so the potential of irritant and allergic reactions is lower. Solutions should be used on the scalp or other hairy areas.

Inadequate prescription size is one of the most frequent problems when treating patients with widespread or chronic relapsing dermatitis. The average adult requires at least 840 g of a moisturizer or topical medication to cover the body once a day for a month. Patients become frustrated at both the expense and inconvenience of refilling prescriptions for 15- and 30-g tubes. Clinicians need to prescribe adequate amounts of topical corticosteroid for the extent of the disease.

Patients must clearly understand how and when to use topical steroids. Proper application of the medication once or twice daily to involved areas can eliminate many potential problems. Applying topical steroids more than twice daily increases the chance of side effects, makes the therapy more costly, and does not increase efficacy. As the dermatitis improves, the frequency of use may be reduced or a less potent topical corticosteroid prescribed.

Topical calcineurin inhibitors

Topical calcineurin inhibitors (pimecrolimus and tacrolimus) are complex macrolide compounds and selectively inhibit cytokine transcription in activated T cells. Because these drugs do not cause skin atrophy, they are useful for facial and eyelid dermatitis and other areas of delicate skin susceptible to side effects of moderate and potent steroids. They should also be considered in patients with chronic extensive AD not controlled with mild-potency corticosteroids when prolonged application of more-potent steroids would risk skin atrophy, adrenal suppression, and other systemic side effects.[68] In some patients it may be necessary to step up to moderate-to-potent topical corticosteroids for 3 to 5 days to control acute flares on the limbs and trunk before stepping down to a calcineurin inhibitor. When the AD remains quiescent, reduction in frequency of application of the calcineurin inhibitor to a few times a week or even to the use of a cheaper mild-potency corticosteroid should be considered.

Tacrolimus is available as an ointment only and is more potent than pimecrolimus, which is available only as a cream.[68] The choice of product is influenced by desired potency and vehicle characteristics. In the United Kingdom, the National Institute of Clinical Excellence approves the use of topical tacrolimus for children older than 2 years with moderate-to-severe dermatitis not controlled by topical corticosteroids but does not recommend it as first-line treatment in mild disease.[69] In the United States, the 0.03% preparation is licensed for children aged between 2 and 15 years, and both the 0.03% and 0.1% preparations are licensed in older patients.

Proactive versus reactive application of topical therapies

Traditional therapeutic paradigms call for reactive use of anti-inflammatory topical treatment applied to all visibly affected skin areas. An alternative approach is proactive therapy, which essentially consists of long-term, low-dose intermittent topical anti-inflammatory therapy (eg, low-to-moderate potency steroids or topical tacrolimus 2 or 3 times weekly) applied to subclinical inflammation that persists in the skin previously affected by AD.[70] Patient visits for clinical control and drug prescription are scheduled at 3- to 4-month intervals. Clinical trials that studied corticosteroid and tacrolimus ointment have shown the benefit of proactive therapy, with an overall improvement, fewer exacerbations, an improved quality of life, and, in severe cases, lower treatment costs.[71-73]

Systemic immunosuppressants and phototherapy

Most patients with AD can be effectively managed with standard therapy: avoidance of trigger factors and topical emollients and corticosteroids/calcineurin inhibitors. However, a small subgroup of patients, despite adequate standard therapy, continues to have troublesome AD and impaired quality of life. These patients should be considered for second-line therapy, including immunosuppressive drugs and phototherapy.

Cyclosporine, a calcineurin inhibitor that blocks T-cell activation, is effective treatment of severe AD.[74,75] The key advantage is the lack of the severe side effects associated with the long-term use of oral corticosteroids. In contrast to many European countries, the Food and Drug Administration has not yet approved cyclosporine for this purpose. The theoretical rational for using cyclosporine is that super-antigen—induced T-cell activation triggered by secondary bacterial skin infection may underlie severe disease. Evidence suggests that cyclosporine is most effective for patients with AD driven by secondary bacterial skin infections rather than allergens, and once the infection has been adequately treated with antibiotics.[76] Cyclosporine is usually started at 5 mg/kg per day in divided doses and weaned by 1 mg/kg per day once a month, discontinuing the medicine completely after approximately 6 months. The drug dose in children and adults is the same, although one study of adults with severe AD suggested that an initial starting dose of 150 mg twice a day may be as effective as 300 mg twice a day.[77]

One randomized placebo-controlled clinical trial suggested that azathioprine may be effective in severe adult AD. Only 37 patients were enrolled and 16 (43%) withdrew (12 in the azathioprine arm).[78] Two trials have compared methotrexate with azathioprine, and both were found to result in a reduction in AD severity, but neither study had a placebo arm.[79,80] Use of systemic corticosteroids such as oral prednisone is not recommended. Although there is often an initial dramatic clinical improvement, rebound flares after discontinuation are common and just as pronounced.[81]

Phototherapy is a second-line treatment for AD in adults but requires personnel expertise for safe, effective delivery.[82,83] Systematic reviews of randomized clinical trials conclude that phototherapy is effective and beneficial in the short-term treatment of AD in adults and adolescents, with high-dose UV-A1 useful as a single therapy for flares, whereas narrow-band UV-B, UV-A, and bath— and UV-A are beneficial for all forms of AD. Meta-analysis has not been possible because disease severity, treatment regimens, and outcome scoring methods varied widely. The long-term effects of phototherapy include an increased risk of developing skin cancer, whereas the short-term adverse effects include itch and acute burns.

Treating secondary skin infections

Systemic antibiotics are often required to treat bacterial skin infections, particularly *S aureus*, which is a common cause of AD flares in children. The choice of antibiotics should be based on sensitivities.[28] It is not advisable to use antibiotics long term because antibiotic resistance will develop. The antiseptics may be effective in reducing bacterial load on the skin and recurrent infections. Silver textiles (eg, DermaSilk, DreamSilk) and bleach baths (dilute hypochlorite) may be helpful in keeping the density of staphylococci low in patients with AD.[84,85] Short-term use of wet wraps in combination with mild (classes VI/VII) topical corticosteroids can be beneficial in the treatment of acute flares or refractory lichenified lesions.[86] However, wet wraps can lead to skin maceration, folliculitis, and secondary infections or rarely adrenal suppression when used for prolonged periods in combination with moderate-to-potent corticosteroids.[87] In this randomized study, 22% of children who used wet wraps for 4 weeks required antibiotics for secondary infection compared with none on the children on conventional treatment.

Infections with *Malassezia* generally respond to topical ketoconazole or miconazole, although the AD usually responds best to topical immunosuppressants.[31,32]

Allergen avoidance

If a specific food is thought to exacerbate the patient's AD, avoidance for 4 weeks can be tried. Professional dietary advice should be sought to ensure that the food is being completely avoided and that the child does not experience nutritional deficiencies, particularly iron-deficiency anemia and clinical or subclinical rickets. After 4 weeks the food should generally be reintroduced, or a physician-supervised food challenge should be performed. Foods should be avoided long term only if they cause a further flare of AD on rechallenge. Infants and young children are most likely to have food-induced exacerbations. Milk, soy, egg, and wheat account for 90% of foods that trigger AD.[88] Food-related AD often resolves with time; therefore, intermittent rechallenging of patients should be undertaken, typically at 6- to 12-month intervals. In patients said to have eczematous reactions to multiple foods, food challenge may confirm that the child is tolerant, particularly when the child is not in the core group listed above. Blood-specific allergen IgE measurements and skin prick tests may support the diagnosis if an IgE-mediated mechanism is suspected.

When there is a clear history of grass or house dust mite exacerbating the patient's AD, the allergen should be avoided when possible. Avoidance strategies are listed in Table IV.

Pruritus

Pruritus is a ubiquitous and poorly tolerated symptom. Sedating antihistamines may offer some symptomatic relief through their sedative effects, but they have little direct effect on the pruritus. Nonsedating antihistamines do not reduce the itch in AD but may be helpful if the patient also has urticaria. Topical corticosteroids and calcineurin inhibitors have been shown on meta-analysis to be more effective than systemic therapies, reducing pruritus scores by one-third.[89] Counselling may be used to try and break the itch-scratch cycle, as well as in adolescents and young adults who may consider their skin disease disfiguring. Relaxation or biofeedback techniques may also be of benefit, especially in patients with habitual scratching.

TABLE IV. Techniques of aeroallergen avoidance in patients with a history suggestive of specific allergen-induced exacerbation

Local barrier
• Use oil-based emollients
• Use dry wraps, bandages, body suits for infants and young children
• Wear long trousers and long-sleeved shirts
• Use dust-proof covers for mattress and pillowcase
Avoidance
• Avoid playing on grass
• Avoid sitting, playing on the carpet
• Minimize carpeting, drapes, and upholstered furnishings
• Declutter sleeping quarters by removing fluffy toys and excess pillows

Alternative therapies

Currently available therapies do not cure AD but rather ameliorate the symptoms. Thus, there is a continuing desire by patients and their caregivers to look for more effective alternatives. One study found that 42% of parents with children with AD had tried alternative therapies, most commonly homeopathy and herbal remedies.[90] Other treatments include aromatherapy, hypnotherapy/biofeedback, and massage therapy. The evidence for the efficacy for most of these therapies comes from uncontrolled case reports and series. Randomized, double-blind, placebo-controlled trials are needed to determine whether any of these approaches have any clinical benefit over and above their placebo effect. The possible exception is Chinese herbal remedies, whereby a number of studies are currently under way in both the preclinical and clinical setting, particularly in acute allergy and asthma, less so in AD, to determine whether they might be developed as disease-modifying agents.[91,92] At present, however, no products are licensed, and clinicians should be aware of the possible contact dermatitis (phytodermatoses) or systemic toxicity from the herbs or in some cases from added immunosuppressive drugs.[93]

Future perspectives in the treatment of AD

Health care professionals are also striving to develop new and improved therapies for AD. Much of the impetus is to try therapies that (1) directly or (2) indirectly inhibit effector immune responses.[94] Examples of the former include biologics such as omalizumab that neutralizes IgE, rituximab that triggers apoptosis of B cells, and etanercept that blocks TNF-α. The evidence for these therapies is currently case reports and series. More work is required to determine whether biologics have a place in routine AD therapy, or whether the cost or side effects outweigh possible benefit, for example, efalizumab, an CD11a antagonist that has been withdrawn partly because of its perceived risk in causing progressive multifocal leukoencephalopathy. A related approach is therapies that indirectly inhibit the immune response by promoting regulatory T-cell function. Subcutaneous and sublingual specific immunotherapies (SITs; eg, to house dust mite, pollen or cow's milk protein) are another approach, whereas use of bacterial adjuvants (probiotics) in an effort to stimulate gastrointestinal tract regulatory T cells is another. Although multiple, large studies have been published, the results are mixed, and at present neither SIT nor probiotics can be recommended in the routine treatment of AD.[95-97] Although SIT is unlikely to be effective for all patients with AD, it may have a role in a subgroup of patients in whom the clinical features suggest that a specific allergen is the predominant

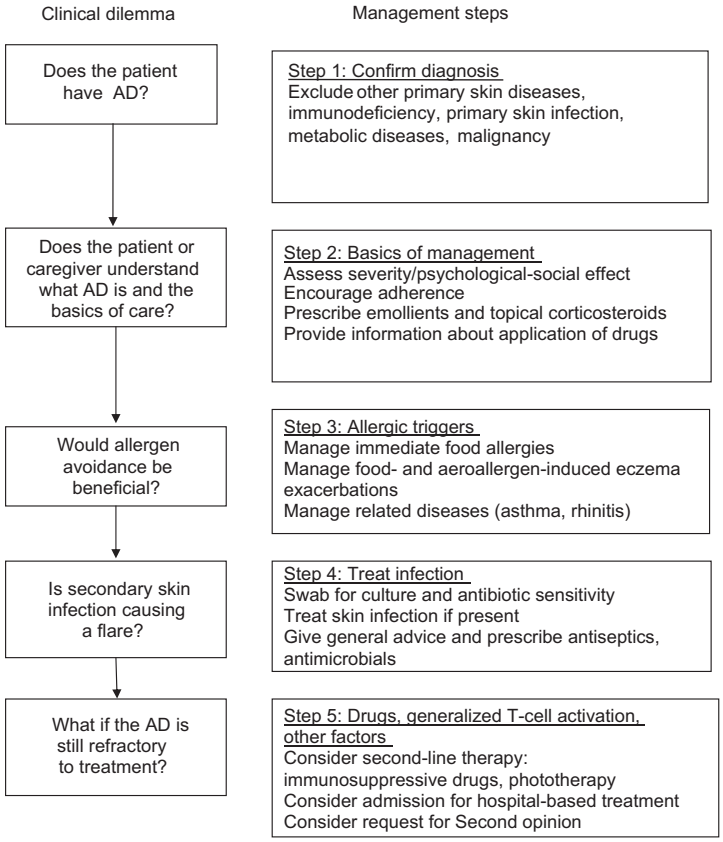

FIGURE 1. Clinical approach to the management of AD.

trigger.[98] In view of the acknowledged importance of skin barrier dysfunction and pruritus in AD, another approach is to develop more effective emollients and nonantihistamine antipruritics, but again these are still very much experimental.[99,100]

SUMMARY AND TREATMENT ALGORITHM

Patients with difficult-to-treat AD can often have their disease controlled if a few simple steps are followed (Figure 1). Before embarking on AD treatment regimes the diagnosis should be confirmed. If the rash is atypical, the patient has additional clinical problems, or an unusual family history, then other primary skin conditions, primary immunodeficiency diseases, metabolic conditions, primary skin infections, and malignancies should be excluded. Once the diagnosis is confirmed, most patients can be successfully managed simply by providing them with information and advice about the condition and how to apply emollients and mild-potency topical corticosteroids. Compliance or lack of it should be assessed. If the physician has insufficient time to impart this information, nursing support and supplementary written information may be invaluable. AD severity should be recorded at each visit to provide objective assessment of response to treatment. Investigators Global Assessment is a simple scoring system. Alternatively, Scoring Atopic Dermatitis and Eczema Area and Severity Index are validated but are more complex to use in a busy clinic.[101]

In an age of super-specialization, it is important not to ignore the patient's other atopic diseases such as asthma and allergic rhinoconjunctivitis and to ensure that they have adequate information about these conditions and their treatment. Food allergens, particularly cow's milk and egg, are most likely to be important in infants and young children, whereas aeroallergens may be clinically relevant in older children and adults. Avoidance of specific foods may have dramatic beneficial effects on selected patients identified on history. There is no evidence for blanket avoidance of, for instance, cow's milk protein in all children with eczema. Although standard allergen-specific IgE measurements and skin prick tests may be useful in confirming the clinical diagnosis of immediate hypersensitivity, they have less relevance in patients in whom foods cause T cell–mediated AD flares. Specific IgE measurements are likely to be falsely positive in the latter situation, particularly in patients with AD with high total IgE concentrations. Diets of children should not be restricted because of specific IgE results unless there is a clear clinical history of the specific foods exacerbating the AD. When a food is removed from the diet to determine its role in causing AD, it should be with the input of a dietician and initially for a period of 4 weeks, after which time the food should be reintroduced to confirm that it has indeed induced the flare. Further studies are required before any recommendations can be made as to the place of allergy patch tests in the management of AD.

For patients with painful, oozing, crusting lesions, particularly if asymmetrically distributed, secondary bacterial infection should be considered as a potential exacerbating factor and treated, usually with oral antibiotics (eg, cephalexin or

flucloxacillin). If the AD is severe and generalized, topical application of ointments may be difficult or impractical. After any secondary infection is controlled, oral cyclosporine treatment might be considered to dampen the excessive T-cell activity, often triggered by bacterial superantigens. Cyclosporine can usually be successfully weaned from a starting dose of 2.5 mg/kg twice a day over 6 months, maintaining control with reintroduction of moisturizers and topical immunosuppressant drugs. Inability to successfully wean the cyclosporine often implies ongoing or recurrent secondary skin infection.

For those patients whose AD is still not controlled, a short period of hospitalization may help to clear up issues of compliance that had not been identified earlier, infection that cannot be cleared by outpatient treatment, or important environmental allergens or stressors. If all the above measures fail, or physicians feel they lack the necessary time or expertise, then a second opinion should be considered.

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