Breaking the cycle: how I manage difficult atopic dermatitis

Romper o ciclo: minha conduta em casos difíceis de dermatite atópica

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Abstract: This review summarizes the general approach and philosophy of managing difficult atopic dermatitis. There are as many regimens as there are physicians, but too many fail to provide patients with adequate relief. This leads to the wasteful alternative - an allergy-seeking behavior that makes caring for these patients even more complicated. If we, as dermatologists, provide rational counseling on prevention and skin care along with effective, stable, anti-inflammatory therapy, our patients may stop seeking irrational approaches. The new flood of information relating to epidermal barrier provides a basis for seeking and treating xerotic conditions earlier during infancy with the hope that the increasing problems with atopic dermatitis and asthma may be lessened with simple and safe measures.

Keywords: Dermatitis, atopic; Dermatitis, atopic/ prevention and control; Dermatitis, atopic/ therapy; Immunologic factors

Resumo: Esta revisão resume a abordagem geral e a filosofia na conduta de casos difíceis de dermatite atópica. Existe uma variedade de tratamentos, assim como de médicos, mas muitos falham e não propiciam um alívio adequado aos pacientes, o que leva a uma alternativa dispendiosa, ou seja, um atitude que visa procurar alergias e complica ainda mais o tratamento desses pacientes. Se nós, como dermatologistas, oferecermos um aconselhamento racional sobre prevenção e cuidados com a pele, junto com uma terapia antiinflamatória eficaz e estável, nossos pacientes irão parar de procurar abordagens irracionalis. O novo fluxo de informações sobre a barreira epidérmica propicia uma base para investigar e tratar as doenças xeróticas em uma fase mais precoce durante o primeiro ano de vida, com a esperança de que os problemas crescentes relacionados à dermatite atópica e asma possam ser aprimorados com medidas simples e seguras.

Palavras-chave: Dermatite atópica; Dermatite atópica / prevenção e controle; Dermatite, atópica/ tratamento; Fatores imunológicos

Profile of Difficult Atopic Dermatitis

Presentations

Dermatologists need little help in managing banal atopic dermatitis (AD). They also need no description of “difficult” AD. Our focus will be the variants that cause particular problems in management. These include the patients with 1) widespread dermatitis which is unrelenting and/or very recalcitrant; 2) hand dermatitis; 3) face, eyelid and scalp dermatitis. 4) Additionally, in each of these categories are the patients who have become dependent upon, and often demanding of, systemic corticosteroids.

These are examples of the more commonly encountered serious challenges when dealing with AD. I will primarily discuss that severely involved patient with widespread, recalcitrant disease because such patients encompass most of the difficulties encountered in caring for AD.

Clinical Assessments

A brief preliminary assessment is essential to 1) confirm the diagnosis1,2 and 2) understand the course of each patient’s condition. 3 For all of our new patients, I start with a short history form that lends itself to diagnosis and to a systematic appraisal of the situation (Chart 1). Age of onset is an important diagnostic feature; late onset suggests the need to at least consider the possibility of another diagnostic entity, such as contact dermatitis or cutaneous lymphoma, especially for therapy unresponsive cases. Present or past involvement of ante-cubital or popliteal flexures is also an important feature for reassuring the diagnosis. A personal or family history of asthma or hayfever is also useful for diagnosis and may influence overall therapeutic choices.

Barrier defects. With the recent groundbrea-king report of 1q21 filagrin mutations in ichthyosis vulgaris and the strong association with AD and

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to five days for superficial infections. Patients are instructed to repeat the treatment at the first sign of flaring. If recurrences are frequent, tetracycline is a reasonable, lower cost alternative for many patients after childhood. For those patients needing longer courses of antibiotics, a one-month course of tetracycline therapy should be considered. Over the past 40 years, in spite of chronic therapy for acne, the rate of *Staphylococcus aureus* resistance to tetracycline has remained low. In such cases, reduction of colonization can also be attempted by application of topical antibiotic to nares, umbilicus, and perineum daily for one week, then once weekly. Topical mupirocin is a popular topical choice, though povidone-iodine probably works as well and is cheaper. Topical antibiotics have not impressed me for direct treatment of the pyoderma of AD; compliance is poor and, in the case of mupirocin, the cost is as great as potent topical steroids.

Recurring HSV or dermatophyte infections are not uncommon but are commonly overlooked and may be another trigger of AD. Yeast infections are rare exacerbants but prominent in the claims of paramedical and alternative practitioners, hence also prominent in the ideations of severe patients who are frustrated and ready to seek any recourse. These patients are reassured by the inquiry into such problems, and occasionally empirical treatment with short-term oral azole antifungals may be a useful ancillary therapy.

**Bathting and moisturizing errors** stand alongside infections as the most important exacerbating factors. They are also the most puzzling of the major management problems for the patients to understand. Each physician has a favorite regimen and that is reflected in the patients’ confusion about their self-care and daily routines. My patients are given the instructions listed in Chart 2. The most difficult problem for patients and many physicians is understanding the oft quoted paradox, "Bathing dries the skin." The obvious answer: True, if the water is allowed to evaporate from the skin, but bathing also hydrates the skin. Therefore, *moisturizer must be applied while the skin is wet*, before leaving the bathroom. The same applies to swimming, hot tubs, etc. – these do no harm if emollients are used promptly.

**Emotional stress** is often a result of, rather than a cause of, severe AD, but stress is one of the few trigger factors that have been scientifically documented. A patient under any emotional burden, frustration, or stressful anxiety is going to be more resistant to therapy. A brief situational assessment is always useful.

**Systemic health problems** are remarkably rare in AD but patients are often concerned about an internal problem. Occasionally thyroid dysfunction is a significant contributor to the recalcitrance of the dermati-
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Chart 2: Bathing and moisturizing

1. Bathing:
   a. Tub bath or wet compresses for severe flaring twice daily for 5 to 20 minutes (until fingertips wrinkle), using lukewarm water only.
   b. Shower; acceptable when skin is under good control or when flare is mild.
2. Avoid washcloths, rubbing, scrubbing or overuse of soap.
3. After bathing, dry off only partially by patting with a towel no rubbing.
4. While some water is still on the skin and within 3 minutes and before leaving the bathroom:
   a) Apply triamcinolone 0.1% or other moderate to potent topical steroid to red, itchy areas;
   b) Apply moisturizer to other areas.
5. Moisturizing should be repeated as often as necessary to keep skin soft throughout the day.

Chart 3: Allergies and Atopic Eczema

1. Patients/parents often think that allergies cause eczema.
2. Parents find it easier to explain eczema to others by calling it an “allergy.”
3. Patients/Parents and caregivers are not educated about differences between eczema and true allergic reactions.
4. Clarify whether we’re discussing eczema or IgE-mediated reactions (e.g. hives, lip swelling, respiratory or GI symptoms).
5. Explain that eczema does not derive from IgE reactions – hives are not eczema.
6. Point out that eczema continues even with avoidance of foods, pets, mites.
7. Consider food challenge tests in recalcitrant, widespread AD in children under 5 years of age.

Skin biopsy is under-utilized in AD. Certainly, patients with recalcitrant severe dermatitis, especially if late-onset, should be considered for biopsy to reassure against development of cutaneous lymphoma or the presence of dermatitis herpetiformis, scabies or other conditions. Likewise, assessment and patch testing for possible allergic contact dermatitis should be considered.

Generally, at the first visit, I outline a plan whereby, if standard therapy does not provide control, further testing will be followed. Depending on diagnostic probabilities (which are always low percentage probabilities), further testing should be considered. Standard patch tests to North American Contact Dermatitis Group (NACDG) allergens or other common contact allergens sets is the first step. Sometimes, patients’ lifelong AD has been replaced by allergic contact dermatitis, usually either from an occupational source or from skin care products. A surprising number of patients have positive patch tests and relevant contact allergy, though testing is difficult, with many irritant and “angry back” reactions.

Skin prick tests or RAST (radioallergosorbent test) studies are usually done through allergist consultation but there is no reason why dermatologists can't perform these tests. These tests are generally not indicated because they provide little relevant or practical information. Hyperthyroidism can complicate the disease and should be ruled out in recalcitrant AD. Obviously, any silent infection or infestation can exacerbate AD and, if these are possibilities, a hematologic exam may be worthwhile, but there are amazingly few cases where laboratory studies are of benefit. Patients who have been treated chronically with systemic corticosteroids should be assessed with baseline bone density studies. Objective evidence of osteopenia is an absolute contraindication to continued oral or intramuscular steroid therapy.

not do these. I take pains to point out to patients and parents that positive tests are only tests and not allergies unless proven by relevant adverse health events. I recommend food tests generally only for young children recalcitrant to therapy. I start with the six most common allergens — egg, milk, peanut, soy, wheat and seafood for RAST/CAP assessment. If there are strong suspicions, I recommend skin prick tests to the panel of allergens of the greatest concern to parents. For aeroallergens, I try to limit testing to about ten inhalants most appropriate to the region and season. These will vary considerably with the geographic locale but, again, discussion with an allergist can detail the best short allergen panel. I always stress to patients/parents that prick tests and RAST determinations are only tests and not allergy and relevance should be seriously questioned. They are not recommended for assessment of AD.

Acute Standard First Visit/Acute Management
Management of AD consists of a) inducing remission; b) maintaining stability of remission and c) rescuing flares to regain remission. Chart 2 can be used as an example of a regimen that commences whenever the patient begins flaring. Typically, twice daily baths or compresses, followed immediately by application of triamcinolone 0.1% ointment for one week are begun at the first visit, even for patients who have been highly dependent upon systemic steroids. If the skin is lichenified or severely inflamed, I will begin with a more potent steroid such as betamethasone dipropionate 0.05% ointment. I use that same drug in a lotion form for scalp dermatitis. It is important to stress that skin hydration is the most essential part of the regimen, affording five- to ten-fold better topical steroid delivery to inflamed sites. When inflammation subsides, typically in three days on the face and seven days on other regions, bath frequency can be reduced to one bath or shower daily. I prefer to schedule a return visit within one week to take advantage of the good results and new optimism and then to add any necessary ancillary therapy. I counsel the patient to expect recurring flares but that those flares can be interrupted with prompt re-initiation of the above regimen. Generally, the sooner the bath routine begins, the quicker control is achieved and maintenance can resume.

Second Visit/Follow-up Visits
Maintenance Therapy
Usually patients require stabilizing therapy to maintain control of dermatitis. Considerable discussion is usually required to give the patient/parent an understanding of the balance between efficacy and safety in the use of topical steroids. When control of flares is achieved (usually three to seven days), I generally limit chronic use of triamcinolone or other mid- to high-potency agents to no more than twice weekly on a given site. I seldom recommend topical hydrocortisone for daily maintenance because it is generally inadequate for controlling difficult AD. I prefer “flare-directed therapy” with steroids that are potent enough to abort exacerbations. Triamcinolone 0.1% is adequate in 90% of instances. I tailor the quantities that will assure continued effective management. Patients must maintain an adequate supply of their topical corticosteroid. Most crises and flares occur when supplies are exhausted. Patients should agree to refill only through their dermatologist so that surveillance against overuse is maintained. I seldom prescribe less than 120 grams (and usually 460 grams for extensively involved adult patients) of these mid-strength maintenance steroids, hence the preference for agents that are bulk priced.

I try to negotiate a moisturizer acceptable to both patient and physician for use on days when steroids are not applied. Typically for dry, winter seasons, petrolatum is optimal. Creams are often adequate and better accepted in hot or humid seasons and climates but creams may not be adequate for patients who live and work in air conditioning, even in the most humid climates. I always tell patients that “lotions are the enemy” because of their irritant potential and the net drying effect of component alcohols and water. Lactic acid and other hydroxyacids are especially irritating and should be avoided in AD.

Clearly the greatest advance in AD therapy since the advent of corticosteroids is the development of the topical calcineurin inhibitors (i.e., tacrolimus and pimecrolimus). While these agents are not as potent as corticosteroids, they provide for excellent second-step maintenance therapy without the risks of atrophy, glaucoma, and hypopigmentation from chronic steroid applications. While derived from immunosuppressive molecules, the calcineurin inhibitors have shown excellent safety from infections and the theoretical concerns of neoplastic progression. FDA warnings and proscriptions are based more on politics than on evidence and considerations of medical needs.

Reasons for Failure / Relapse
When patients cannot maintain control of their dermatitis with standard topical care, I find useful an inventory of possible reasons for this failure (Chart 4). Noncompliance is a major problem, especially in adolescents and teenagers. This basic problem has been
compounded by phobias directed against corticosteroids and calcineurins and these phobias, in turn, have been agitated by irresponsible marketing of bland and unquestionably effective ancillary approaches.

Ancillary Therapies
Most patients with severe AD will need stabilizing therapies in addition to antibiotics and topical steroids. These should be considered when patients are not well-controlled in spite of optimal moisturizing, adequate topical steroids and testing to preclude allergy. Alternatives or ancillary therapies roughly in order of practical choices are listed below.

UVB therapy. The physician has several choices including standard UVB, narrow-band UVB, combination UVA plus UVB, psoralen photochemotherapy (PUVA) or natural sunlight. The latter can be helpful but is often associated with increased heat causing sweating and itching. Frequent water immersion or spraying is needed to avoid complications. UVB is generally inadequate for all but mild AD. PUVA is effective but slow, expensive and fraught with flare reactions and long-term aging and cancer risks. My first choice is either narrow band UVB or combination therapy with UVA, 3 to 5 J, plus UVB, 30 to 50 mJ initial dose and increasing by 0.5 J UVA and 10 mJ UVB each treatment with a frequency of two to three times weekly. Patients typically begin to respond more quickly than with PUVA, often within two to three weeks and, while photoreactions can occur, they are far less frequent.

Grenz radiotherapy. While obviously not an option for widespread dermatitis, Grenz ray can be very helpful for persistent hand, foot and scalp problems which are often difficult to control, even with frequent applications of high or super potency topical steroids. Dosing varies widely but 200 to 400 r every one to two weeks for four to six treatments will usually provide at least temporary remissions. When hand dermatitis begins to recur, I use topical 0.1% 8-methoxypsoralen ointment plus UVA for maintenance.

oral antifungals. Studies in Scandinavia have suggested that hypersensitivity to pityrosporon species may be a chronic exacerbant to AD. I consider a two-week therapeutic trial of itraconazole or fluconazole worthwhile in recalcitrant AD. These are especially reassuring to patients who have questioned the possibility of yeast causation. If patients do well with a two-week trial, the therapy can be continued, but generally dosing only once weekly for up to three months. Prescriptions are limited and not refilled without lab chemistry to guard against liver toxicity.

Psychotherapy/stress management. Many patients can benefit from psychological counseling on ways to deal with the disruptive stresses that add to the severity of their AD. Serious pathology is unusual, hence the objectives can often be directed toward coping with situational problems that add to the burdens of chronic disease.

Phosphodiesterase inhibitors. Theophylline, 300 mg b.i.d. for five days, can provide mild relief at beginnings of flares. Longer duration therapy appears to generate tachyphylaxis. Perhaps for similar reasons, the efficacy of papaverine has been marginal. Newer, high potency inhibitors show considerable promise for topical use and may be developed as alternatives to steroids.

Antihistamines. The main value of these agents is the sedative effect but some patients find antipruritic benefit from hydroxyzine, 10 to 100 mg q.i.d., or doxepin, 10 to 50 mg daily. For the rhinoconjunctivitis symptoms which often accompany AD, non-sedating antihistamines may be helpful but they have no anti-pruritic benefit.

Vitamins and "natural" substances. Some patients find improvement with oral vitamin E in a dose of 200 to 400 U daily. Claims made of efficacy for Vitamin C in childhood AD do not appear to have been substantiated by controlled trials. Topical vitamin D3, calcipotriol, has been suggested for treatment of psoriasis and it may provide some relief of AD, particularly for hand dermatitis. Retinoids have consistently proven highly irritating, even for atopics with only respiratory disease and no dermatitis. Exceptions may be the anti-inflammatory effects of RXR-activating "rexinoids" such as topical hexarotene and oral 9-cis-retinoic acid, both of which have shown efficacy in hand eczema.

Chinese herbal mixtures have been reported useful for some individuals with severe AD, but much may depend upon the herbal practitioner’s experience with AD. Evening primrose oil, borage oil, and other

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**Chart 4: Reasons for failure of acute management**

1. Noncompliance – especially steroid and CI phobias
2. Inadequate physician counseling on topical therapy
3. Depletion of topical steroid supply
4. Psychological factors / stress, depression
5. Resistant staphylococcal infections
6. Herpes simplex infection
7. Fungal infection
8. Upper respiratory and other viral syndromes
9. Undetected food allergy
10. Scabies
11. Thyroid disease
12. Steroid allergy
13. Sweating / exertion
14. Photosensitivity

compounds rich in gamma linolenic acid have had many claims of theoretical rationale and clinical efficacy but, in spite of many years of trying, advocates have failed to show objective evidence of benefit.

**Immunomodulators**

**Cyclosporin A.** This immunosuppressant is highly effective in treatment of severe AD and should be considered for patients who are unresponsive to optimal topical therapies, and especially for those dependent upon systemic corticosteroids. For healthy, normotensive persons with no renal or cardiovascular disease, cyclosporin A, 5 mg/kg in a single daily dose, will usually provide prompt relief of itching and reduction of inflammation within two to five days. If they have not responded in this period, I occasionally raise the dose to 7 mg/kg until remission is achieved. The dosage can then be slowly tapered, usually to the range of 3 mg/kg. While I generally do not request blood levels for monitoring therapy, some relatively unresponsive patients may show low trough levels and may be best managed with periodic blood levels. I advise patients, before starting, that treatment will be limited to three to six months because of side effects which include hypertension, reduced renal function (usually reversible) and interstitial fibrosis. My approach is to begin tapering dosage within one month and begin combination UVA/UVB therapy that will allow continued control of AD when cyclosporin A must be discontinued. Blood pressures should be checked weekly and chemistry panels biweekly. Nifedipine should be used for moderate increases in blood pressure.

**Systemic corticosteroids.** This is a controversial topic but my observations suggest that 1) systemic steroids are widely overused; 2) patients on systemic steroids can be treated with topical therapy along with other measures listed above; 3) osteopenia (see above), cataracts and other complications are occurring in many patients; 4) most physicians use meager initial doses of oral steroids, providing inadequate suppression that results in the need for too prolonged therapy. Because AD is a chronic disease, use of systemic steroids, other than brief (two to six days), occasional courses of prednisone, carries the liability of demands for prolongation of this high-risk therapy. Tachyphylaxis occurs and discontinuation always leads to rebound flaring. Typically, for severe flares or for patients exhausted by unremitting eczema, I prescribe 30 to 40 mg twice daily for two days, halving the dose each two days for a total of six days. Patients resume topical care the last two days on prednisone. I consider intramuscular steroid dosing unnecessary and risky for treatment of such a chronic disease.

**Azathioprine.** This immunosuppressant drug may be marginally safer than the above two agents but it usually is slow in onset and considerably less effective than cyclosporine, and characterized by a relatively high rate of hepatic and other side effects. A trial of therapy in adults might be considered, using doses of 100 to 200 mg daily for one month.

**Interferon-gamma.** This biological response modifier is effective in the majority of patients with severe AD, probably favoring younger individuals. It can be quite helpful in patients not controlled with cyclosporin but it is exceedingly expensive and must be given by subcutaneous injection. Flu-like side effects can be reduced by daily or alternate day bedtime dosing in combination with acetaminophen. Symptoms tend to tolerate with continued use and safety is probably greater than for the immunosuppressants, though long-term safety is not established.

**Other Biologics**

In contrast to psoriasis, very few studies have looked at these agents in AD. An open study of infliximab in Europe found few positive effects on the dermatitis. A recent three-month pilot study of efalizumab in ten patients with very severe AD noted definite improvement in most during the first four to eight weeks, but these positive effects dissipated for most of the patients during the later stages of the study. Generally few adverse effects were noted aside from one patient who developed progressive thrombocytopenia that continued after discontinuing the drug and required systemic corticosteroid therapy until the problem eventually resolved six months off the drug.

**Mycophenolate Mofetil**

This immunosuppressive agent has been used for several years in treatment of difficult AD and it can be quite helpful in some patients. Dosing can be initiated with 1500 mg/day in adults but in some patients, twice higher doses are required to induce remission.

**Hospitalization**

Patients who have failed other forms of therapy might best be hospitalized to provide clearing of skin inflammation and allow for patch testing, prick testing and food avoidance and challenge. For many severe patients, there is simply no other way to prepare for testing since it cannot be done while patients are on immunosuppressives, nor when the skin is widely inflamed. Past observations indicate that even severe inflammation subsides spontaneously with minimal treatment when patients are hospitalized but modern cost-control restrictions necessitate active therapeutic measures to speed clearing. These include the acute care measures (Chart 2) but without antihistamines which interfere with skin prick testing. Chloral hydrate (0.5 to 1 gm) or benzophenone agents should be...
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