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Atopic dermatitis – all you can do from the outside

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Summary

Atopic dermatitis (AD) affects both the epidermal barrier and the immune system and, as such, therapy needs to address both. Skin cleansing supported by emollients and moisturizers is the primary topical therapy when treating patients with AD. However, it should be remembered that the direct use of emollients on inflamed skin is poorly tolerated and that the flares need to be treated effectively, usually by topical corticosteroids (TCS) and/or topical calcineurin inhibitors (TCI). This contribution outlines a number of strategies for effectively managing AD, from reactive therapy using TCS and TCI to proactive therapy. Proactive therapy is an alternative, evidence-based, immunologically founded treatment approach, based on the fact that normal-looking, nonlesional skin of patients with AD is not normal. The advantage of the proactive approach is that the patients are in control of their disease and are actively involved in its management. The avoidance of external irritants is recommended wherever possible.

Atopic dermatitis (AD) is a common chronic inflammatory skin disease with increasing prevalence.¹ The pathophysiology of AD probably involves an interaction of both environmental and genetic factors which cause abnormalities to occur in the epidermal barrier and the immune system.² Taking into account that the clinical phenotypes of AD (i.e. 'extrinsic' AD and 'intrinsic' AD) have the same skin lesions and distribution patterns, it is not surprising that the treatment guidelines for AD can be applied to both forms. This is further justified by the fact that both the barrier-initiated mechanism (outside-inside hypothesis) and the primary immunological abnormality mechanism (inside-outside hypothesis) involve an epidermal barrier defect. Thus, it is logical to suggest that external treatments are used to repair this defect.

Skin cleansing

The primary aim of topical treatment of atopic skin is to cleanse the skin. Besides the obvious hygienic purpose (i.e. the elimination of crusts and scales), cleansing is important as barrier dysfunction in patients with AD can lead to abnormal bacterial colonization. Pathogenic bacteria, such as *Staphylococcus aureus*, may be harmful either in themselves or by acting as antigens and/or superantigens, triggering immunoglobulin E (IgE)-specific antibody production. Approximately 99% of patients with AD present with *S. aureus* colonization, and half of these are toxin producing. Pathogenic staphylococci can also cause further damage to the skin barrier due to their proteolytic activity. Lastly, increased barrier dysfunction can result from the action of cystatin A, a cysteine proteinase inhibitor of house dust mites proteases, which may contribute to break down corneodesmosomes in the skin. All these reasons justify the need for careful hygiene.

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Other secondary infections, such as yeasts (*Malassezia spp.*), dermatophytes and viral infections have also been implicated as disease factors in AD. A special phenotype of AD called 'head and neck AD' is often seen in adolescents and young adults. In these individuals, sebaceous secretion is very active and capable of stimulating the growth of lipophilic yeast. In addition, strong alkaline detergents (mostly bubble soaps) also contribute to the deterioration of the skin barrier. Indeed the acidic pH (~ 5.0) of the normal skin surface provides ideal growth conditions for normal cutaneous microflora; in atopic skin, the surface pH is higher (~ 6.0) and enhances the protease function leading to barrier dysfunction, as well as downregulation of lamellar body secretion.

In summary, we recommend frequent (every day or every other day) baths or showers with lukewarm water for 2–5 min using mild (amphoteric or oil-based) detergents for most patients with AD. Cleansing the skin relieves the symptoms, diminishes the bacterial concentration and prepares the skin for the necessary medications. Long, warm baths with normal soaps or bubble baths, are often not well tolerated by patients and almost invariably provoke an aggravation of the disease. Cleansers, with or without antiseptics, should be evaluated carefully. Strong concentrations or inappropriate galenic forms are unsuitable, whereas low (e.g. $\text{KMnO}_4 = 1/10\,000$ in water) or very low (e.g. sodium hypochlorite = $5/100\,000$ in water) concentrations of antiseptics are commonly used safely and successfully.

Emollients

With dry skin being one of the main symptoms of AD and part of its definition, it seems logical that emollients and moisturizers are considered by most experts to be the basic treatment for disturbed skin barrier (i.e. the preferred skin care therapy).³ Besides filaggrin deficiency, other factors such as a lack of stratum corneum intercellular lipids and an inadequate ratio between compounds (cholesterol, essential fatty acids, ceramides),⁴ together with a protease–antiprotease imbalance, can lead to raised transepidermal water loss and increased transepidermal penetration of exogenous molecules as a consequence.

Despite there being a consensus on the use of emollients as the mainstay of maintenance therapy, it is important to remember that the direct use of emollients on inflamed skin is poorly tolerated. This is a common mistake made, in most instances, by paediatricians and by those who 'hate' topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI) who forget that it is mandatory to treat the acute flare first. This mistake derives from the premise that emollients are always useful and never 'negative'. However, emollients are effective only once the following two conditions have been obtained: the acute flare is under control (no more oozing) and the formulation of the emollient is correct. (Note: fatty ointments are more persistent on the skin but are, in general, less tolerated.) While the presence of acute eczema can be distinguished easily by anyone, choosing the 'right' emollient is a difficult task and can still justify the expression: 'the art of dermatology'. In summary, there is no question that, for an experienced dermatologist, emollients are the mainstay of maintenance therapy.⁵ The weak points of this therapy are two-fold: tolerability and cost.

Tolerability

At present, there are hundreds of different, specifically designed emollients and moisturizers for AD available on the market, all with different formulations, and all with their own 'pros' and 'cons'. Therefore, it can sometimes be difficult for a dermatologist to decide which product to choose. One possible solution is to apply two different products to either side of the body (the intraindividual medications technique) and observe any possible signs and symptoms for 20 min. After this period, all possible acute intolerances or idiosyncrasies should have presented and it will be easier to prescribe the right emollient for that patient and gain their adherence to treatment. It is important to remember that emollients and moisturizers cannot cure AD flares; in fact they can sometimes exacerbate AD when applied at the 'wrong' moment (e.g. the sole use of emollients without sufficient topical anti-inflammatory therapy increases the risk of disseminated infections, which are already raised in patients with AD).

Cost

Although the cost of emollients is not a scientific issue *per se*, in practice it is important to consider.⁶ The cost of high-quality (low in contact allergens) emollient therapies often restricts their use because such therapies are considered to be nonprescription drugs (except, for example, in Finland and, partially, in France) and the quantities required are usually high (150–200 g per week in young children and up to 500 g in adults). Indeed, it is important to remember that emollients and moisturizers should also be applied generously to normal skin to prevent penetration by irritants or allergens and relapse of eczema. In other words, the application of an emollient should become part of a patient's daily regimen. From this perspective, the cost of emollients is a major problem for most patients and limits the possibility of self-medication at home.

Avoidance recommendations

Together with ensuring good hygiene, avoidance recommendations are, for some patients, as important as formal medication.⁷ This means that, in order to assess the severity of a definite case of AD and, consequently, to design an individual therapeutic plan, one has to verify whether specific and nonspecific provocation factors are present, active and capable of maintaining or aggravating the disease. Fortunately, albeit infrequently, the avoidance of some triggers like mechanical irritants (e.g. wool, rough textiles), chemical (e.g. acids, bleaches, solvents, certain food ingredients such as alcohol, additives or vasoactive amines), biological (e.g. pets, house dust mites, pollens, microbes) and physical (e.g. tobacco smoke or traffic exhaust), can transform a patient with severe AD into a mild–moderate one. However, this does not take into account the significant, and not yet solved problem of food allergy, which is not addressed in this paper. In our experience, irritant contact dermatitis (ICD) is a common event in infants in which a follicular (and itchy) dermatosis is present on the trunk. In these cases, ICD is usually the result of voluntary or involuntary application of various substances (e.g. residual of the detergent used to wash fabrics, body powders or body lotions,

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etc.). In school children, adolescents and adults, the role of allergic contact dermatitis (ACD) is more important but is frequently underestimated, supporting the importance of systematic patch testing in atopic patients of this age. Together with the common contact sensitizers (metals, fragrance, preservatives, dyes, etc.), one should remember the possible contact allergy to TCS!

Topical anti-inflammatory therapy

Topical treatment remains pivotal in the management of AD but its efficacy depends on three fundamental principles: sufficient strength, sufficient dosage and correct application. Topical treatments should always be applied after the skin has been cleansed. To date, TCS remain the first-line anti-inflammatory treatment, and should be applied on inflammatory skin according to the needs of the patient (pruritus, sleeplessness, new flare). Numerous substances are available in a variety of formulations. TCS are grouped by potency: group I (mild), II (moderate strength), III (potent) and IV (very potent), which should be known to prescribers. It should be noted that the American system is the reverse and is divided into seven classes, ranging from class I (super potent) to class VII (low potency). Usually, the acute phases of AD are controlled with one to two applications per day of a potent TCS cream. This treatment will suppress the objective signs (erythema and oozing) and control the subjective symptoms (itch and sleep loss) within a few days, even though tapering should not be initiated before the itch has disappeared. Dose tapering should be gradual to avoid withdrawal rebound; tapering strategies consist of using a less potent corticosteroid on a daily basis, or keeping a more potent one while reducing the frequency of application (intermittent regimen).

Patients with acute oozing and erosive lesions, and children in particular, vary in their responses to the galenic form (cream, ointment, etc.) of medication. Some patients with very inflamed lesions do not tolerate standard topical application, and may first be treated with the so-called 'wet wrap(s) technique' (WWT) until the oozing stops.⁸ WWT is usually performed using a topical corticosteroid based-cream and a double layer of cotton bandages, with a moist first layer and a dry second layer. The topical medication can be applied as usual on the skin, or previously diluted in lukewarm water in which the first layer is moistened. The use of WWT for up to 14 days (usually 2–3 days) is a safe intervention treatment for severe and /or refractory AD and is almost always characterized by a dramatic improvement in the disease. What is normally overlooked by people (doctors included) is the fact that topical therapy is time consuming (WWT, of course, is even more time consuming) and some techniques (e.g. WWT) have to be practically illustrated by doctors or nurses, at least for the first application. For many decades, textbook chapters and position papers on AD have recommended a topical anti-inflammatory treatment of the visible skin lesions only.^{9,10} After cessation of visible lesions, all anti-inflammatory therapy had to be tapered down and stopped completely in favour of an exclusive therapy with barrier-stabilizing emollients. Consequently, this treatment concept is now referred to as 'reactive therapy'.¹¹ TCS and TCI are well-established agents for reactive therapy of AD.^{12–14} However, because long-term control of the recurrent flares is a more important goal than the treatment of acute flares, novel therapy strategies have had to be established.

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Proactive therapy is an alternative, evidence-based, immunologically founded treatment approach, which has emerged in recent years. It is based on the fact that normal-looking, nonlesional skin of patients with AD is not normal. Firstly, the skin barrier function of nonlesional AD skin is damaged, as witnessed by an increased transepidermal water loss through the stratum corneum.^{15–17} Filaggrin mutations have been identified as the genetic background in a subgroup of patients with AD.¹⁸ Secondly, the fraction of long-chain fatty acids in the lipid bilayer of the stratum corneum is reduced by 60% in nonlesional AD skin compared with healthy skin.¹⁹ Thirdly, histological examination shows an activation of the venules, as well as a low-grade lymphocytic infiltration in nonlesional AD skin.²⁰ Finally, the density of high-affinity IgE receptors on the surface of the epidermal Langerhans cells, an important receptor for the IgE-mediated allergen presentation, is significantly upregulated in nonlesional AD skin.^{21,22} In summary, nonlesional AD skin looks normal to the naked eye, but harbours subclinical inflammation.

Proactive therapy of atopic dermatitis – definition and history

Proactive therapy is defined as long-term, low-dose, intermittent application of anti-inflammatory therapy to previously affected skin, together with daily application of emollients to unaffected areas.²³ This ‘minimal therapy for minimal eczema’ therapy is continued after clearance of the visible eczema at a low frequency – usually twice weekly.²³ Data from different trials with TCI and TCS have confirmed a significant improvement in skin lesions, a significant reduction of flares and improved quality of life for patients.

From a patient’s perspective, the disease no longer controls the patient’s actions, but the patient himself or herself is actively controlling his or her disease.¹⁷ Another important aspect is the scheduling of the control visits: in proactive therapy, these are planned beforehand and are time-contingent, whereas control visits in a reactive treatment take place on a symptom-contingent basis following acute relapses.¹⁷

The first clinical trial of intermittent anti-inflammatory therapy was published in 1999.²⁴ The general concept of an immunobiologically based, time-contingent, low-dose anti-inflammatory therapy with behavioural therapeutic background was presented in 2007 in Dresden²⁵ and published in detail as ‘proactive treatment’ in 2009.¹⁷ This term has been chosen deliberately in accordance with the writings of Viktor Emil Frankl²⁶ and the existing nomenclature of a physician-initiated scheduling of patient contacts in behavioural therapy.¹⁷ The concept of proactive therapy is nowadays recommended in all European treatment guidelines for AD.^{12,27,28}

The clinical evidence for this recommendation is mostly based on trial data from nine larger, randomized, placebo-controlled trials, which have assessed the efficacy of TCS and TCI. Useful outcome parameters for comparison of these clinical trials are the median time to first flare or the percentage of flared patients after a fixed time period (e.g. 3 months), but only if these are assessed comparing the active drug and placebo control groups.¹¹ The sole percentage of flare-free patients at the end of a clinical trial is not a useful parameter to study drug efficacy, as it is highly influenced by the duration of the trial and the severity of the patient group rather than being based on the efficacy of the study drug.¹¹

Proactive therapy of atopic dermatitis – clinical trial data

Van Der Meer *et al.*²⁴ tested fluticasone propionate in a 16-week proactive treatment regimen in 90 patients with moderate and severe AD. The proactively treated patients showed significantly fewer eczema flares. Hanifin *et al.*²⁹ evaluated the optimal frequency of application of fluticasone propionate in 348 patients with mild to severe AD. The risk for flare development under proactive treatment was 7.7-fold lower than that under placebo therapy. Berth-Jones *et al.*³⁰ assessed fluticasone propionate in a proactive treatment approach with 295 patients over 16 weeks. The recurrence-free period under proactive therapy was more than twice as long as under reactive treatment. Glazenburg *et al.*³¹ studied the biweekly application of fluticasone propionate in a 16-week, placebo-controlled, randomized study of 75 moderately to severely affected children with a similar result, as the flare risk in the proactive group was less than half of the reactive group.

Wollenberg *et al.*³³ studied the proactive use of tacrolimus on 257 adult patients with mild, moderate and severe AD in a European long-term multicentre trial over 12 months. A double-blinded, randomized, placebo-controlled 1-year maintenance treatment phase was conducted with twice-weekly application of tacrolimus or placebo ointment and liberal use of emollients. The proactively tacrolimus-treated patients showed significantly fewer flares, a significantly reduced flare duration and a significantly longer median flare-free time.³³ Thaci *et al.*³⁴ conducted a similar tacrolimus study with children in an analogue study design over 12 months with similar efficacy. A retrospective subgroup analysis of the patients with moderate to severe AD – the currently licensed indication for tacrolimus ointment – was published based on the combined data set of the Wollenberg³³ and Thaci³⁴ trials in 2010.³⁵ Paller *et al.*³⁶ tested the thrice-weekly proactive use of tacrolimus in a 40-week trial against placebo and demonstrated a significantly longer median time to first flare in the proactively treated patients than in the control group. Breneman *et al.*³⁷ tested the thrice-weekly proactive application of tacrolimus with similar results.

Peserico *et al.*³² tested methylprednisolone aceponate in a proactive approach over 16 weeks in adult patients with AD. The low risk of flare in the placebo group (66%) argues for an extremely mild disease population in this study.

In conclusion, clinical experience and published trial data uniformly indicate the suitability of TCI and TCS for proactive therapy.¹¹ The profile of side-effects does not depend on the proactive or reactive use of the substances, but on the respective potency of TCI and TCS. None of the drugs tested showed an increased risk of cutaneous infection if applied proactively.¹¹ Although skin atrophy is a known side-effect of improper reactive TCS application, this has not been observed during proactive application of fluticasone propionate.²⁹ The twice-weekly application of tacrolimus 0.1% ointment is sufficient to keep patients in a tolerant, nonburning state.¹¹ Patients with mild, moderate and severe AD will profit from proactive therapy, especially with tacrolimus ointment.^{33,38} All patients with AD should, according to Viktor Emil Frankl,²⁶ become proactive with regard to their disease – which means becoming active before a minor problem becomes a situation.

Skin protection

While it is widely known that some fabrics, such as wool, used for clothing may exacerbate skin conditions due to their rough fibres, few doctors are aware of the potential benefits that special clothing can offer. In the last two decades, functional textiles with intrinsic properties, such as antibacterial activity, have been gaining importance in medical applications. In AD, specially designed fabrics may support classic treatment and improve quality of life: clothing can be an effective barrier against flare-inducing factors and persistent scratching, especially in children, allowing more rapid improvement of the eczematous lesions. Together with silver-coated fibres (especially popular in the U.S.A. some years ago), a special silk fabric (Micro Air, DermaSilk®), a synthetic silk-like fabric (DermaTherapy®)³⁹ and ZnO-functionalized textile fibres⁴⁰ have been shown to be suitable for patients with AD.

Conclusion

We believe that topical therapy can treat the vast majority of cases of AD. This involves ongoing appropriate cleansing of the skin supported by emollients and moisturizers, with the use of TCS and TCI for acute flares. While the reactive therapy approach to AD treatment has been used up until now, an alternative proactive method of treating AD has recently emerged, which allows patients to have active control over their disease. There is also an increasing body of published trial data indicating the suitability of TCS and TCI for proactive therapy, further supporting this approach to treating AD.

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