

REVIEWS

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Difficult to control atopic dermatitis

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Abstract

Difficult to control atopic dermatitis (AD) presents a therapeutic challenge and often requires combinations of topical and systemic treatment. Anti-inflammatory treatment of severe AD most commonly includes topical glucocorticosteroids and topical calcineurin antagonists used for exacerbation management and more recently for proactive therapy in selected cases. Topical corticosteroids remain the mainstay of therapy, the topical calcineurin inhibitors tacrolimus and pimecrolimus are preferred in certain locations. Systemic anti-inflammatory treatment is an option for severe refractory cases. Microbial colonization and superinfection contribute to disease exacerbation and thus justify additional antimicrobial / antiseptic treatment. Systemic antihistamines (H1) may relieve pruritus but do not have sufficient effect on eczema. Adjuvant therapy includes UV irradiation preferably of UVA1 wavelength. "Eczema school" educational programs have been proven to be helpful.

Keywords: Atopic dermatitis, Eczema, Therapy, Guideline

Introduction

Atopic dermatitis (AD, atopic eczema, eczema) is an inflammatory, chronically relapsing, and intensely pruritic skin disease occurring often in families with atopic diseases (atopic dermatitis, bronchial asthma and/or allergic rhino-conjunctivitis) [1]. Less than 10% are regarded as severe cases because of disease intensity and extent (SCORAD > 40) or refractory to treatment. Reasons for severe courses of AD are based on individual (e.g. genetic, barrier function, allergies) risk factors and sometimes on therapeutic problems like misunderstandings with regard to topical treatment. Management of exacerbated AD is a therapeutic challenge, as it requires efficient short-term control of acute symptoms, without compromising the overall management plan that is aimed at long-term stabilization, flare prevention, and avoidance of side effects.

Exacerbations may sometimes uncover relevant provocation factors, for example contact allergy, or infection. This synopsis on refractory AD excludes the general principles of AD treatment like basic skin care and management of

food allergy, as these main strategies are published elsewhere in guidelines [2]. Nevertheless, these basic rules have to be included in the management of all severe cases, too. Figure 1 summarizes the general treatment options.

Contact allergy

The role of contact allergy in AD patients is frequently underestimated [3,4]. The frequency of contact sensitization in AD, ranging from 41% to 64% according to recent observations, supports the importance of systematic patch testing in atopic patients, adults and children. The most common contact sensitizers are metals, fragrance, preservatives, dyes, neomycin, and lanolin, but contact allergy to topical glucocorticosteroids is also not rare in AD patients.

Contact sensitization may worsen the skin condition of AD patients and influence the course of the disease. Moreover, sensitized AD subjects may respond to very low concentrations of contact allergens, because of their impaired skin barrier function and hyper-reactivity to irritant stimuli enhancing contact reactions.

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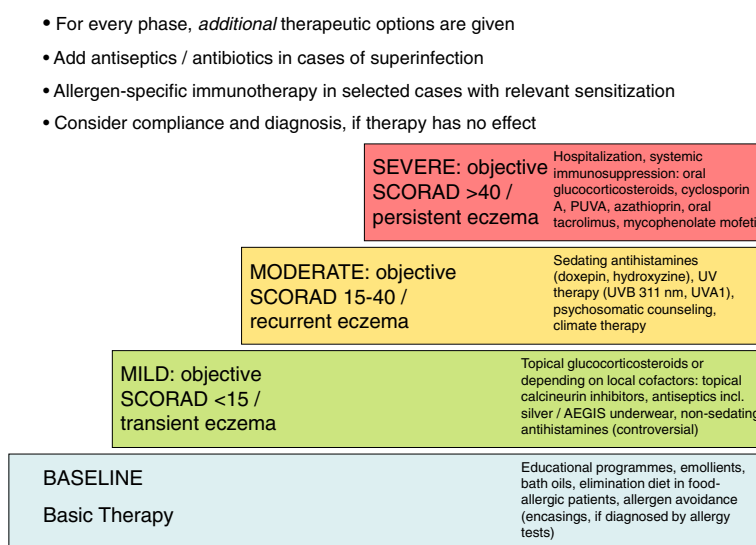


Figure 1 Recommendation for treatment of adult eczema / atopic dermatitis according to graded severity (modified from 44).

Topical anti-inflammatory treatment

Topical treatment

The use of wet-wrap dressings with (diluted) corticosteroids for up to 14 days (usually applied for 3 days) is a safe crisis intervention treatment of severe and/or refractory AD with temporary systemic bioactivity of the corticosteroids as the only reported serious side-effects [5,6]. By tradition, anti-inflammatory topical therapy has been administered to lesional skin only and has been stopped or tapered down once visible lesions were cleared. This traditional, reactive approach has in the last years been challenged by the proactive treatment concept, which is defined as a combination of pre-defined, long-term, low dose, anti-inflammatory treatment applied to previously affected areas of skin in combination with liberal use of emollients on the entire body and a predefined appointment schedule for clinical control examinations [7,8].

Corticosteroids

Topical corticosteroids (TCS) are a first line anti-inflammatory treatment, applied on inflammatory skin lesions according to needs (pruritus, sleeplessness, new flare). Proactive therapy for flare prevention is also possible with TCS. Topical corticosteroids are grouped by potency, which should be known to prescribers. Potent and very potent corticosteroids (group III and IV) are more likely to cause depression of adrenal function than group I (mild) and II (moderate strength) treatments, but their systemic effects will decrease more quickly due to more rapid restitution of the skin barrier [9,10]. However, potency ranking of topical steroids in some countries including the US is the reverse of the European system

with class I (superpotent) to class VII (low potency). For severe AD, group II and group III (EU system) glucocorticosteroids are recommended. Itch is the key symptom for evaluation of response to treatment, and tapering should not be initiated before the itch has disappeared. Dose tapering should be gradual in order to avoid withdrawal rebound. Tapering strategies consist in using a less potent corticosteroid on a daily base, or keeping a more potent one while reducing the frequency of application (intermittent regimen).

Topical calcineurin inhibitors

Both topical calcineurin inhibitors (TCI), tacrolimus ointment (0.1% and 0.03%) and pimecrolimus cream (1%), are licensed for topical eczema treatment. Various aspects of these drugs have been reviewed in detail [11]. The efficacy of both formulations has been demonstrated against placebo in clinical trials for short term [12,13] and long term use of these substances [14,15]. In addition, proactive tacrolimus ointment therapy has been shown to be safe and effective for up to one year in reducing the number of flares and improving the quality of life in adult patients and children [16,17]. The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a corticosteroid with intermediate activity [18], while the latter is clearly more active than 1.0% pimecrolimus cream [19].

Antihistamines

Systemic antihistamines (anti H1) are widely used in acute flares against itch, however few controlled studies are available [20]. Antihistamines may be helpful in decreasing pruritus and permit sleep during flares. In

this setting, sedative anti H1 molecules such as hydroxyzine are recommended by clinicians as helpful. Concerning the newer non-sedating H1R specific antihistamines, controlled studies did not show significant effects on eczema.

Anti-bacterial and antimycotic therapy

A number of defects in innate and adaptive immunity may explain the high rate of cutaneous colonization with *Staphylococcus aureus* (up to 90% in moderate to severe eczema) in AD [21]. There is evidence that a decrease in microbiome diversity is associated with an increased colonization with *S. aureus* as well as increase in disease activity. Antibiotic eradication of *S. aureus* may therefore not always be an appropriate long-term strategy, especially with regard to the increasing prevalence of antibiotic resistance [22-24]. In particular topical antibiotics should not be used for longer periods in the treatment of AD. There is evidence for an association of *S. aureus*-derived superantigens with disease exacerbation [25,26], supporting early observations that the density of *S. aureus* colonization in AD is significantly correlated with clinical severity [27], and that patients with severe AD may improve (but not be cured) by anti-staphylococcal treatment [28]. In general, improvement of eczema by anti-inflammatory therapy (i.e. TCS, TCI, UV) decreases *S. aureus* colonization.

Other secondary infections, such as yeasts, dermatophytes, and streptococcal infections have also been implicated as disease factors in AD (for a review, see [22]). Intense, fleshy erythema in skin folds of children with a flare of AD may warrant a search for streptococcal skin infection. In general, signs of secondary infections should be treated if present. Ketoconazole and ciclopiroxolamine are proposed for topical treatment of "head and neck" AD, often associated with *Malassezia sympodialis* superinfection [29,30].

Phototherapy

Except UVA1, which was shown to be effective in managing AD flares, phototherapy is not indicated in the acute stages of AD, but apt to treat chronic, pruritic, lichenified forms. However, it should not be prescribed in patients who experienced a worsening of their dermatosis during sun exposure. Usually, phototherapy is part of a total treatment plan in addition to topical anti-inflammatory and antimicrobial therapy. As second-level treatment it is used especially in adults. Phototherapy in children younger than 12 years should not be applied under normal circumstances.

Present UV sources include equipments able to emit selective spectra of radiations

- Broadband UV (UVA+UVB = 290–400 nm)
- Narrow-band UVB (nbUVB = peak:311–313 nm)
- UVA1 (340–400 nm).

nbUVB has been indicated for chronic-moderate forms of AD [31] and is currently preferred to broadband UV because it is less erythemogenic, while high dose UVA1 has been prescribed for more severe phases [31].

Systemic anti-inflammatory therapy

Non-response to adequately applied topical therapy is rare, and systemic anti-inflammatory treatment should be limited to severe cases in which the potential of topical treatment (or of patient compliance) has been exhausted. An actual overview of the different options has been published [32]. Corticosteroids are rapidly effective, but should only be used for a few weeks, for severe acute exacerbations, because of the many long term side-effects. In severe chronic cases consider starting another systemic anti-inflammatory therapy while tapering the corticosteroid.

The usefulness of both cyclosporin (3–5 mg/kg/day) and azathioprine (2.5 mg/kg/day) has been well documented in clinical trials with children and adults [33-36]. Cyclosporin A therapy is rapidly effective, but has a narrow therapeutic index and requires a close follow-up of renal function. It is an approved substance for systemic treatment of AD in many countries and is frequently used for systemic immunosuppressive therapy in AD.

Azathioprine has a slower onset of action and is not always well tolerated. Low TPMT (thiopurinemethyltransferase) activity is associated with an increased myelotoxicity of azathioprine, but patients at risk can be identified by pre-treatment screening for TMTP activity [35].

Mycophenolate mofetil (2g/day) seems to offer a comparatively more favourable safety profile and its usefulness in severe AD is documented in both prospective and retrospective studies [37-39], but remains to be assessed in larger randomized trials.

Methotrexate is used by many clinicians as an alternative treatment. Only a few studies have documented its effect and more randomised trials are needed [40].

Biologic agents (biologicals) present new therapeutic tools in the treatment of recalcitrant AD. They specifically target inflammatory cells and mediators, respectively, and thus may inhibit pathogenically relevant pathways. A number of case reports and pilot studies have been published recently, however representative, randomized, placebo controlled studies evaluating the efficacy and safety of biologicals in AD are still not available. Approaches resulting in reduced T cell activation using agents such as alefacept (fusion protein of lymphocyte function antigen (LFA)-3 (CD58) and immunoglobulin (Ig)G, rituximab (anti-CD20 antibody) and efalizumab (anti-CD11a antibody, no longer available) have been shown to be effective in selected patients with moderate to severe AD and were mentioned in guidelines [2,41-44].

Educational programs and counselling

In the last decade, education programs for patients and parents were established in different countries in Europe, but also in North and South America (see www.opened-dermatology.com). Standardized interdisciplinary programs involving dermatologists, paediatricians, psychologists / psychosomatic counsellors, and dietary counselling have been demonstrated to support the improvement of subjective and objective symptoms, and optimize medication use in patients, and result in a significant gain in quality of life [45]. Participation in one of these programs is highly encouraged.

Competing interests

U. Darsow has been speaker, investigator and / or been a member of advisory boards for Allergopharma, ALK-Abello, Bencard, GSK, Hermal, Novartis, Stallergenes, Stiefel. M. Deleuran is speaker, investigator and/or advisor for Leo Pharma, Pierre Fabre, MEDA and Astellas. J. Ring conducted clinical trials or research for ALK-Abello, Allergopharma, Allmiral-Hermal, Astellas, Bencard, Biogen-Idec, Galderma, GSK, Leo, MSD, Novartis, Phadia, PLS Design, Stallergenes. A. Wollenberg has received research funding and lecture honoraria from, conducted clinical trials for, or is a paid consultant to Astellas, Basilea, Galderma, GSK, L'Oréal, MEDA, Merck, Novartis, Pierre Fabre, MSD. Other authors declared that they have no competing interests.

Authors' contributions

UD coordinated and participated in the consensus process and drafted the manuscript. AW, DS, AT, TW, AO, CG, AS, MD, AMC, FG, JL, SS and JR participated in the consensus process and drafted the manuscript. All authors read and approved the final manuscript.

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