

GUIDELINES

Guidelines for treatment of atopic eczema (atopic dermatitis) Part I

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Abstract

The existing evidence for treatment of atopic eczema (atopic dermatitis, AE) is evaluated using the national standard Appraisal of Guidelines Research and Evaluation. The consensus process consisted of a nominal group process and a DELPHI procedure. Management of AE must consider the individual symptomatic variability of the disease. Basic therapy is focused on hydrating topical treatment, and avoidance of specific and unspecific provocation factors. Anti-inflammatory treatment based on topical glucocorticosteroids and topical calcineurin inhibitors (TCI) is used for exacerbation management and more recently for proactive therapy in selected cases. Topical corticosteroids remain the mainstay of therapy, but the TCI tacrolimus and pimecrolimus are preferred in certain locations. Systemic immune-suppressive treatment is an option for severe refractory cases. Microbial colonization and superinfection may induce disease exacerbation and can justify additional antimicrobial treatment. Adjuvant therapy includes UV irradiation preferably with UVA1 wavelength or UVB 311 nm. Dietary recommendations should be specific and given only in diagnosed individual food allergy. Allergen-specific immunotherapy to aeroallergens may be useful in selected cases. Stress-induced exacerbations may make psychosomatic counselling recommendable. 'Eczema school' educational programs have been proven to be helpful. Pruritus is targeted with the majority of the recommended therapies, but some patients need additional antipruritic therapies.

Conflict of interest

A. Alomar has been speaker for Almirall, Astellas, Leti. T. Bieber has been advisor, speaker or investigator for ALK Abelló, Astellas, Bencard, Galderma, Glaxo SmithKline, Leo, Novartis, Stallergenes. U. Darsow has been speaker, investigator and/or been a member of advisory boards for Allergopharma, ALK Abelló, Bencard, GSK, Hermal, Novartis Pharma, Stallergenes, Stiefel. M. Deleuran has been a speaker, participated in clinical trials and/or been a member of advisory boards for Merck, Novartis, Astellas, Leo Pharma, NatImmune, Pergamum, Pierre Fabre and Janssen-Cilag. A.-H. Fink-Wagner received honorarium from Pharmaxis and Chiesi during the last 3 years and was employed before that by Nycomed. J. Ring has been advisor, speaker or investigator for ALK Abelló, Allergopharma, Almirall/Hermal, Astellas, Bencard, Biogen-Idec, Galderma, Glaxo SmithKline, Leo, MSD, Novartis, Phadia, PLS Design, Stallergenes. S. Ständer was or is adviser, speaker and/or investigator for Aesca Pharma, Almirall/Hermal, Astellas Pharma, Beiersdorf AG, Birken, Essex Pharma, GSK, Pierre Fabre, Maruho, 3M Medica, Mundipharma, Novartis Pharma, Serentis, and Serono. Z. Szalai is investigator of clinical trials for Astellas, Novartis, Pfizer, Abbott, Pierre Fabre. A. Taieb has received consulting and clinical trial honoraria from Pierre Fabre, Astellas, Almirall/Hermal, Leo and Novartis. T. Werfel has been advisor, speaker or investigator for ALK Abelló, Astellas and Novartis. A. Wollenberg has received research funding and lecture honoraria from, conducted clinical trials for, or is a paid consultant to Astellas, Basilea, GSK, Loreal, Merck, Novartis, MSD. Other authors declared no conflict of interest.

Introduction

Atopic eczema (AE; atopic dermatitis, eczema, 'Neurodermitis' in German speaking countries, endogenous eczema) is an inflammatory, pruritic, chronic or chronically relapsing skin disease occurring often in families with other atopic diseases (bronchial asthma and/or allergic rhinoconjunctivitis¹).

Atopic eczema is one of the most common skin diseases which affects up to 20% of children and 1–3% of adults in most countries of the world.² AE is often the first step in the development of other atopic diseases as rhinitis and/or asthma.

In the diagnoses of AE several criteria have been established.^{3,4} There is no pathognomonic laboratory biomarker for diagnosis of AE, since the most typical feature, the elevation of total or allergen-specific IgE levels in serum or the detection of IgE-mediated sensitization in the skin test, is not present in all individuals suffering from AE; for this latter group the term 'intrinsic' (non-IgE-associated) AE has been introduced to distinguish it from 'extrinsic' (IgE-associated) forms of AE.⁵ This controversy in terminology is going on until today^{1,6} and has practical implications with regard to specific avoidance strategies in the management of this disease. In the aetiopathophysiology of AE several aspects have to be taken into consideration:

Apart from strong genetic influence (80% concordance in monozygous twins, 20% in heterozygous twins), there are characteristic features in pathophysiology as follows:

- Immune deviation towards Th2 in the initiation phase with consequent increased IgE production
- Deficient skin barrier function ('dry' skin) due to abnormal lipid metabolism and/or epidermal structural protein formation (filaggrin mutation, protease inhibitor deficiency, etc.)
- Abnormal microbial colonization with pathogenic organisms such as *Staphylococcus aureus* or *Malassezia furfur* (compared with *Staphylococcus epidermidis* in normal

individuals) and subsequent increased susceptibility to skin infection

- Obvious strong psychosomatic influence with an imbalance in the autonomic nervous system with subsequent increased production of mediators from various inflammatory cells (e.g. eosinophilic leucocytes).

In the management of AE these various pathogenic reactions have to be considered in an individual approach regarding the abnormal reactivity patterns found in the individual patient suffering from AE.

After establishing the diagnosis of AE, the severity of the disease has to be determined. The classical method is the 'Scoring of Atopic Dermatitis' (SCORAD) developed by the European Task Force of Atopic Dermatitis (ETFAD). The SCORAD has been modified by several authors.⁷ AE with a SCORAD higher than 40 is generally regarded as 'severe', whereas AE with a SCORAD below 20 can be regarded as 'mild'.

It has to be mentioned that the majority of cases with AE can be regarded as 'mild' with 10–20% of patients suffering from severe eczematous skin lesions⁷; this percentage seems to be higher in the adult AE population. In the following, the most important strategies in management and medication will be briefly discussed.

Methods

The guideline committee decided that these guidelines should strictly concentrate on therapeutic regimens and omit longer chapters on clinical entity, diagnosis or pathophysiology of the disease.

Base of the guideline

The existing evidence-based National guideline from Germany,⁸ the HTA report⁹ as well as the position statement of the ETFAD¹⁰ were compared and evaluated using the national standard

Appraisal of Guidelines Research and Evaluation (AGREE). The committee decided that all the documents fulfilled enough criteria to be used as the base of the new evidence-based European Guidelines on Treatment of Atopic Eczema.

Data base and literature search

Newer literature published after the German Guidelines⁸ and the ETFAD Position Statement¹⁰ was searched using medline, EMBASE and the Cochrane Library.

Evaluation of the literature

The evaluation of the literature focused on the efficacy of the therapeutic modality and was assessed with regard to the methodological quality of the study according to the well-known criteria of evidence (Table 1).

Based on the grade of evidence recommendations were classified (Table 2).

Consensus process

The committee designated especially important areas as those requiring consensus. The consensus process consisted of a nominal group process and a DELPHI procedure. Consensus conferences were held in Berlin October 2009, Cavtat May 2010, Munich July 2010 and Goteborg October 2010, where the sections regarding consensus were discussed by the entire guidelines group following a formal consensus process.

External review

According to the EDF standard operation procedure all European dermatological societies were invited to review the guidelines prior

to the last internal review. The comments of the participating societies were forwarded to the chapter authors and considered during the last internal review.

Update of the guidelines

These guidelines will require updating approximately every 5 years. Based on new HTA reports the development of a S3 guideline might be advisable.

Target group

This guideline has been prepared for physicians, especially dermatologists, paediatricians, general practitioners and all specialists taking care of patients suffering from AE. Also patients and relatives should be able to get reliable information and evaluation with regard to evidence-based therapeutic modalities.

Basic treatment of disturbed skin barrier function and emollient therapy ('skin care')

Emollient therapy and skin care

Dry skin is one of the main symptoms of AE and part of the definition. There is now scientific evidence in humans and mice of genetically driven skin barrier anomalies that facilitate allergen penetration into the skin with an increased proneness to irritation and subsequent cutaneous inflammation. Filaggrin deficiency is the best defined anomaly, which gives rise to a deficiency in small water binding molecules resulting from normal filaggrin catabolism.¹¹ Besides that, a lack of stratum corneum intercellular lipids and an inadequate ratio between compounds (cholesterol, essential fatty acids, ceramides) enhance trans-epidermal water loss leading to epidermal micro-fissuring. Barrier disruption leads to inflammation, and protease-antiprotease imbalance is a crucial intermediate step.¹²

Cleansing and bathing

The skin must be cleansed thoroughly, but gently and carefully to get rid of crusts and mechanically eliminate bacterial contaminants in the case of bacterial super-infection. Cleansers with or without antiseptics (the duration of action of antiseptics is very limited, thus mechanical cleansing is probably more important) in non-irritant and low allergen formulas available in various galenic forms (syndets, aqueous solutions) may be used. It is easier to perform this first stage of gentle cleansing of skin on the nappy mattress rather than directly in the bathtub in infants. A further cleansing followed by a rapid rinse is performed in the bath (27–30°C). The short duration of the bath (only 5 min) and the use of bath oils (last 2 min of bathing) are aimed at avoiding epidermal dehydration. Topical emollients are preferentially applied directly after a bath or a shower following gentle drying when the skin is still slightly humid.

Adding sodium hypochlorite to the bath-water seems very important because of its bacterial count inhibiting activities. It may be advised to every treatment in AE. A recently published

Table 1 Grades of evidence

| | |
|----|---|
| 1a | Metaanalysis of RCT |
| 1b | Single RCTs |
| 2a | Systematic review of cohort studies |
| 2b | Single cohort studies and RCTs of limited quality |
| 3a | Systematic review of case control studies |
| 3b | Single case control study |
| 4 | Case series, case cohort studies or cohort studies of limited quality |

RCT, randomized clinical trials.

Table 2 Classification of strength of recommendation

| Recommendation strength | Evidence grade |
|-------------------------|----------------|
| A | 1a, 1b |
| B | 2a, 2b, 3a, 3b |
| C | 4 |
| D | Expert opinion |

study¹³ showed that children who took a bath using half a cup of bleach per full standard tub were relieved of their AE related itching. The bleach apparently had very little odour. Salt baths may be beneficial because of removing the dead keratolytic material.¹⁴ In heavily impetiginized or ichthyotic skin salt baths are useful.

Emollient therapy

The direct use of emollients on inflamed skin is poorly tolerated and it is better to treat the acute flare first. Emollients are the mainstay of maintenance therapy. Hydration of the skin is usually maintained by at least twice daily application of moisturizers with a hydrophilic base, e.g. 5% urea. The use of barrier ointments, bath oil, shower gel, emulsions or micellar solutions enhancing the barrier effect is also recommended. The cost of high-quality (low in contact allergens) emollient therapies often restrict their use because such therapies are considered to be non-prescription drugs (except, e.g. Finland, where prescription and reimbursement are usual) and the quantities required are usually high (150–200 g per week in young children, up to 500 g in adults). A better molecular and biochemical knowledge of the skin in AE should provide access to barrier improving topical agents. There is limited evidence-based proof for the use of emollients.¹⁵

Ingredients and possible risks of emollients

Glycerol seems better tolerated (less smarting effect) than urea plus sodium chloride.¹⁶ Usually, the recommendation is to use emollients immediately after bathing and soft pad drying. A small study suggests that emollient applied alone without bathing have a longer duration as measured by capacitance.¹⁷

Propylene glycol is easily irritating in young children aged less than 2 years and should not be used in these young children. There is evidence that the large preventive use of emollients containing allergens such as peanut¹⁸ or oat¹⁹ may increase the risk of skin sensitization and allergy. Only emollient preparations devoid of proteinaceous allergens and haptens (contact allergy) should be used, especially in the most vulnerable age group before the age of 2 years.

Sole use of emollients without sufficient topical anti-inflammatory therapy involves a considerable risk for disseminated bacterial and viral infection, which is already increased in AE patients.²⁰

Evidence of efficacy

Certain moisturizers could improve skin barrier function in atopsics and reduce skin susceptibility to irritants²¹. Lodén *et al.* found in a comparative study between a glycerol-containing cream and placebo an improvement over time in both groups indicating the importance of emollient treatment in AE. Another study in adult AE patients suggested an effect of coconut oil on *Staphylococcus aureus* carriage.²²

Evidence of steroid sparing effects

Short-term (3–6 weeks) Several studies in children (e.g. ^{23,24} and one in a mixed children-adult population²⁵ showed a variable, but consistent evidence of short-term steroid sparing effect in mild to moderate AE.

Long-term maintenance therapy Maintenance of stable disease can be obtained with emollients used twice weekly or more frequently in a subset of patients, after an induction of remission with topical corticosteroids. Several studies derived comparable results for intermittent emollient therapy and time to relapse, using comparable study designs in adults and children.^{26,27} Regimens for basic/maintenance therapy are still awaiting validation based on systemic reviews and a Cochrane review (Oranje in prep.).

Recommendations

Emollients should be prescribed in adequate amounts and these should be used liberally and frequently, e.g. for emollient cream/ointment a minimum of 250 g per week. Emollient bath oils and soap substitutes should also be used. In winter time more lipid ingredients are preferable (3b, C).

A regular use of emollient has a short- and long-term steroid sparing effect in mild to moderate AE. An induction of remission with topical corticosteroids is required first (2a, B).

The rapid progress in better molecular and biochemical knowledge on the predisposing AE background should provide access to scientifically designed barrier improving topical agents, which indeed correspond to a major part of the aetiologic treatment of the disease and are not limited to a mere symptomatic one (4, D).

Avoidance strategies

Many patients are desperate when they hear from their physicians that AE is not 'curable'. It is important to explain the difference between the genetic predisposition towards hypersensitive and dry skin which cannot be 'cured' today and the acute eczematous skin lesions which can very well be treated and disappear. The identification of individual provocation factors is crucial in the management of AE and their avoidance allows longer phases of remission or total clearance of symptoms. In avoidance recommendations one has to distinguish between primary, secondary and tertiary prevention measures. Among provocation factors, specific and non-specific elicitors have to be distinguished.

Non-specific provocation factors

Numerous factors and substances from the environment can irritate the sensitive skin of patients with AE and can elicit eczema flares. They may be physical, like mechanic irritants (e.g. wool), chemical (acids, bleaches, solvents and water) or biological (microbes) in nature. Information on unspecific irritants and their role in aggravating eczema is a crucial prerequisite for long-term

management of patients with AE. Here also the adequate skin care and hygiene procedures in cleansing and dressing have to be discussed with the patient (see also Part II, 'Educational Program, Eczema School').

Negative effects of air pollutants upon the development and maintenance of AE, like tobacco smoke or volatile organic compounds (VOCs) in indoor environments and traffic exhaust in the outdoor air have to be mentioned. There is evidence from epidemiological trials that exposure to indoor chemicals, such as formaldehyde, increases skin barrier disturbance;²⁸ a mixture of volatile organic compounds has been shown to increase the intensity of atopy patch test (APT) reactions to aero-allergens in patients with AE.²⁹ Exposure to traffic exhaust has been shown to be associated with an increased risk to develop AE in pre-school children.^{30,31}

Exposure to environmental tobacco smoke measured as urinary cotinin/creatinin ratio was associated with a significant elevated risk to develop AE, which was especially pronounced in children of parents with an atopic background.³²

Avoidance strategies regarding tobacco smoke as well as traffic exhaust exposure in young children have been introduced in the recent S3 guideline for primary prevention of atopy in Germany.^{33,34} Certain food ingredients like alcohol, additives or vasoactive amines may also trigger eczematous skin flares³⁵; see also 'Food Allergy'.

Specific allergen avoidance

Aeroallergens Aeroallergens have been shown to elicit eczematous skin lesions. In a rather high percentage of patients with AE the APT is positive (30–50%).³⁶ Most common airborne allergens eliciting eczema are derived from house dust mites of the species *Dermatophagoides pteronyssinus* and *D. farinae*. Also mold exposure in damp indoor environment has been found to be associated with increased eczema risk.³³

House dust mites are living in a complex eco-system consisting of air humidity, temperature and organic material. They accompany humans and are most commonly present in dust from mattresses or bedroom floors. Normal cleaning measures help only little in decreasing house dust mite allergen present in the room. Encasings of mattresses and beddings protect humans from mites contained in mattresses. There are also mite-proof pyjamas ('eczema overalls'). There are some studies showing a clear-cut benefit from house dust mite avoidance strategies in the improvement of AE.³⁷

Rehabilitation programs in mite-free environments – like in alpine climate – have shown to lead to significant and long-lasting improvement of AE.^{38–40} Pollen in the outdoor air also can elicit flares of AE as has been shown in a nested case control study in preschool children.⁴¹ Pollen avoidance is difficult under everyday conditions in most parts of Europe except when air conditioning with pollen filters is used in the indoor

environment. In high altitude mountain climate pollen counts are usually lower than in the average living areas.

Animal epithelia Many patients are already aware that contact with animals is leading to a deterioration of the skin symptoms. Although in former times avoidance of pets was a central feature in primary prevention recommendations for atopy, this has been modified as follows: cat epithelia exposure is regarded by most authors as a risk factor, so it should be avoided. There is no evidence that dogs increase the risk of AE in children. Once a patient is sensitized and allergic to a pet, avoidance is absolutely necessary. There is no evidence that pet keeping has a preventive effect in primary prevention of AE among normal population.

Dietary recommendations See chapter 'Dietary intervention'.

Clothing and textiles Smooth clothing and avoidance of irritating fabrics and fibres is essential in the avoidance of primary skin irritation. Too occlusive clothing inducing heat sensations should be avoided. Early ear-piercing and use of nickel-releasing jewellery has been found to be associated with a significantly elevated risk of nickel contact allergy in young girls.⁴² Special recommendations have to be given in individual counselling programs with regard to the choice of profession. There is common consensus that occupations with marked skin-damaging activity or contact with strongly sensitizing substances should be avoided by patients with AE.⁴³

Recommendations

There is some evidence that house dust mite avoidance strategies, especially encasings, can reduce house dust mite and house dust allergen content in indoor air and by that improve AE. The latter is controversial, since some RCTs did not show this effect (2b, B).

There is evidence that house dust mite avoidance and high altitude climate may give benefit to patients suffering from AE (2b, 3b, B).

There is a rationale for using protective clothes (eczema overalls), although good studies are missing (–, D).

In spring and summertime pollen exposure may exacerbate AE in the air-exposed skin areas; pollen avoidance measures can be recommended (–, D).

When classical patch tests are positive, relevant contact allergens should be avoided (–, D).

Dietary intervention

Food allergens

Among food allergens, cow's milk, hen's egg, wheat, soy, tree nuts and peanuts are most frequently responsible for eczema or exacerbation in infancy.⁴⁴ In older children, adolescents and adults pollen related food allergy should be taken into account.^{45,46}

Different types of clinical reactions to food have been described in patients with AE: Early reactions, such as urticaria, gastrointestinal or respiratory symptoms occur within 120 min after the administration of the allergens. Late phase responses, manifesting as eczematous lesions, occur after 2–48 h or some days. After oral food challenge, about 50% of children with AE who reacted to food showed both immediate and delayed reactions and 15% showed worsening of eczema only.⁴⁷ The personal history is often not helpful predicting late reactions to food with a positive predictive value of only 30% as opposed to 80% for immediate reactions.

Sensitizations to food can be identified by means of *in vivo* tests [skin prick tests (SPT), prick–prick tests] and *in vitro* tests (serum specific IgE). In addition, patch tests proved to be useful for studying delayed food-related skin responses. *In vitro* tests are valuable when SPT cannot be applied (e.g. dermographism or UV- and drug induced skin hypo-reactivity, eczema at the test site, lack of compliance for SPT in infancy, etc.). Moreover, *in vitro* specific IgE to food allergens give better quantitative data for the grade of sensitization which helps to estimate the probability of the risk of a clinical reaction (although precise decision points are not available) and it offers the opportunity to test single recombinant allergens which may have a better diagnostic specificity than testing with food extracts for some foods (e.g. omega-5-gliadin in wheat allergy, Gly m 4 in pollen-related soy allergy).

Atopy patch tests are performed with self-made food material applied to the back with large test chambers for 48–72 h. Food APT are not standardized for routine use.⁴⁸ So far, APTs have demonstrated to improve the accuracy of skin testing in the diagnosis of allergy to cow's milk, egg, cereals, and peanuts in AE patients.^{49–55} Whereas immediate-type reactions are associated with SPT positivity, delayed ones are related to positive responses to APTs. However, food challenge is not replaced by patch testing.⁵⁶

The double-blind placebo-controlled food challenge is considered the gold standard for diagnosing food allergy.⁵⁷ In AE, the evaluation of delayed reactions after 24 or 48 h by trained personal is mandatory as stated by a recent position paper of the EAACI.⁵⁸ Challenge tests based on repeated exposure to food enable the assessment of delayed adverse responses.^{49,50,54,55} The major flaw is that they do not offer the opportunity to exclude placebo reactions and/or coincidental influences of other trigger factors of AE during the prolonged challenge period.

Unfortunately, the effects of *dietary interventions* on the course of AE have been studied in a few controlled studies only so far.

In a systematic review⁹ eight randomized, controlled studies studying the effect of an elimination diet on existing AE were identified and summarized in the following way:

- Elimination diets are difficult to be performed even in a motivating atmosphere during a clinical study.

- The drop-out-rate in AE studies is particularly high in studies on diets.
- There is no convincing evidence that a milk- or egg-free elimination diet is beneficial in general when unselected groups of patients with AE were studied.
- There is no evidence for a benefit in the use of elementary or few food restricted diets in patients with AE.

A recently published systematic review identified a single prospective controlled study that supports the notion that a direct elimination diet (in the study: egg exclusion) may be beneficial for the course of AE in sensitized patients with clinical symptoms upon ingestion of eggs.⁵⁹

Recommendations

Patients with moderate to severe AE should observe a diet eliminating those foods that elicited clinical early or late reactions upon controlled oral provocation tests (2b, B).

Topical anti-inflammatory therapy

Topical treatment

Effective topical therapy depends on three fundamental principles: sufficient strength, sufficient dosage and correct application. Topical treatment should always be applied on hydrated skin, especially when using ointments. The emollient should be applied first when it is a cream, 15 min before the anti-inflammatory topical is applied and when it is an ointment 15 min after. Patients with acute, oozing and erosive lesions, and children in particular, sometimes do not tolerate standard topical application, and may first be treated with 'wet wraps' until the oozing stops. They are highly effective in acute eczema and improve tolerance. The use of wet-wrap dressings with diluted corticosteroids for up to 14 days (usual is rather up to 3 days) is a safe crisis intervention treatment of severe and/or refractory AE with temporary systemic bioactivity of the corticosteroids as the only reported serious side-effects.^{60,61} Even without wet wraps, topical therapy is time consuming: patients should plan 30 min for one session. One well-conducted treatment per day is usually sufficient; oozing eczema may require a few days with higher treatment frequency.

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 predefined, 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.⁶² The first trial with intermittent topical steroid use was published already in 1999.⁶³ The proactive, usually twice weekly treatment regimen is started after all lesions have successfully been treated by an intensive, usu-

ally twice daily treatment approach in addition to ongoing emollient therapy for previously unaffected skin. Clinical trial data are available for a number of steroid products as well as for tacrolimus ointment.^{63,64}

Application amount of topical anti-inflammatory therapy should follow the finger-tip unit (FTU) rule. A FTU is the amount of ointment expressed from a tube with a 5-mm diameter nozzle and measured from the distal skin-crease to the tip of the index finger (~0.5 g); this is an adequate amount for application to two adult palm areas, which is approximately 2% of an adult body surface area.

Glucocorticosteroids

Topical glucocorticosteroids are a first-line anti-inflammatory treatment, applied on inflammatory skin according to the needs (pruritus, sleeplessness, new flare). Numerous substances are available in a variety of formulations. Evidence-based anti-inflammatory effects in AE were reported by different investigators.^{26,63,65} With mild disease activity, a small amount of topical corticosteroids twice to thrice weekly (monthly amounts in the mean range of 15 g in infants, 30 g in children and up to 60–90 g in adolescents and adults), associated with a liberal use of emollients generally allows a good maintenance keeping SCORAD values below 15–20. Such monthly amounts of even potent topical steroids usually do not have adverse systemic or local effects.

Topical corticosteroids are grouped by potency, which should be known to prescribers. In addition, there are different generations of substances, which may differ in their risk-benefit ratio. 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.⁶⁶ 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 to avoid withdrawal rebound; tapering strategies consist of using a less potent corticosteroid on a daily base, or keeping a more potent one while reducing the frequency of application (intermittent regimen). One well-conducted, correctly dosed treatment per day is sufficient.^{67,68} The most constructive way to spare steroids and avoid steroid-related side-effects is not to spare them during acute flares, but through consequent baseline emollient skin care combined with early anti-inflammatory intervention to stabilize the disease and prevent treatment-intensive flares.⁶⁹ Usually one daily application of topical steroids is sufficient.

The special aspects and potential adverse effects of topical corticosteroids in pregnancy are reviewed in a recent S3 guideline.⁷⁰ Twice weekly application of fluticasone significantly reduced the risk of relapses of eczema in a 'proactive' strategy.^{26,63,65}

The combination of topical corticosteroids with topical calcineurin inhibitors (TCI) does not seem to be useful. At least in paediatric patients with severe AE, the efficacy and safety profile of

pimecrolimus cream 1% combined with fluticasone were similar to that of fluticasone alone.⁷¹

In a recent paper, it has been observed that glucocorticoids inhibited the double-stranded RNA (dsRNA)-induced release of thymic stromal lymphopoietin in the atopic cytokine milieu at much lower concentrations than calcineurin inhibitors, suggesting that they could be effective in the treatment of AE when exogenous or endogenous dsRNA is involved in the pathogenesis.⁷²

Recommendations

Topical corticosteroids are important anti-inflammatory drugs to be used in AE, especially in the acute phase (–, D).

Topical corticosteroids have a significant effect improving skin lesions compared to placebo (1b, A).

Topical corticosteroids with an improved risk-benefit ratio are recommended in AE (–, D).

The efficacy of topical glucocorticosteroids (1b, A) can be increased by using wet wraps (1b, A).

Proactive 'therapy', e.g. twice weekly application in the long-term follow-up may help to reduce relapses (1b, A).

TCI

Both TCI, tacrolimus ointment and pimecrolimus cream, are licenced for topical eczema treatment. Various aspects of these drugs have been reviewed in detail.^{73,74} The efficacy of both formulations has been demonstrated against placebo in clinical trials for short-term^{75,76} and long-term use of these substances.^{77,78} In addition, proactive tacrolimus ointment therapy has been shown to be safe and effective for up to 1 year in reducing the number of flares and improving the quality of life in adult patients and children.^{79,80} The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a corticosteroid with intermediate activity,⁸¹ while the latter is clearly more active than 1.0% pimecrolimus cream.⁸²

Safety data of both TCI have been reported in many clinical trials, demonstrating the safety of these drugs in daily routine use. The most frequently observed side-effect is a transient warmth sensation or transient burning at the application site during the first days of application.^{75,82} It starts about 5 min after each application of the drug and may last up to 1 h, but intensity and duration typically decrease within 1 week to zero.⁸³ Generalized viral infections such as eczema herpeticum (EH) or eczema molluscum (EM) have been observed during topical calcineurin inhibitor treatment,^{84,85} but a high number of clinical trials failed to demonstrate an increased frequency or showed only a transient increase (reviewed in^{86–89}). In contrast with corticosteroids, none of the TCI induces skin atrophy.^{90,91} This favours their use over topical corticosteroids in delicate body areas such as the eyelid region, the perioral skin, the genital area, the axilla region or the inguinal fold and for topical long-term management. Two safety aspects of TCI regarding potentially increased malignancy rates are

discussed from time to time in the scientific community and the media – lymphoma risk and white skin cancer risk. Clinical and preclinical data do not indicate an increased risk of the induction of lymphoma over a period of 6 years⁹² or photocarcinogenicity for TCI,^{93,94} but since the continuous oral administration of the calcineurin inhibitor cyclosporine is associated with an increased photocarcinogenicity risk in solid organ transplant patients, UV protection e.g. with sunscreens has been advised.⁸¹ The interpretation of the lymphoma risk should consider the fact, that a diagnosis of AD as such is associated with an increased risk for lymphoma.⁹² A recent letter sent out on EMEA directive in 2012 from the manufacturing company of tacrolimus ointment to all dermatologists in the EU could have induced again a feeling of potential long-term risk of malignancies, but in fact it did not communicate any new safety data, and indeed reassured physicians to follow the current label of tacrolimus ointment. According to the latest knowledge, there is no scientific evidence of an increased risk for malignancy due to a topical treatment with calcineurin inhibitors.^{94a} The use of TCI under wet wraps or on erosive lesions may increase systemic absorption.

The efficacy of long-term monotherapy with tacrolimus ointment has been shown in children and adults.^{81,82} Less data are available for children under 2 years of age.^{95,96} Pimecrolimus cream has been studied in infants and children in a combination regimen with topical corticosteroids,^{97,98} the latter being given if a flare occurred. Both TCI are approved in the EU from 2 years of age and above. Highquality long-term safety data have recently been published from a 4-year tacrolimus and 26 weeks pimecrolimus study.^{99,100} The cost effectiveness of proactive therapy with topical tacrolimus has been demonstrated for moderate AE and is even higher in severe AE in a recent study with adult patients,^{100a} whereas the cost effectiveness of first-line treatment with TCI has not been shown conclusively. However, in children with AE, twice-weekly treatment with tacrolimus 0.03% ointment has been observed to reduce the number of flares and to prolong time spent free from flares with no additional cost in children with moderate AE, and may be cost-saving in those with moderate and severe AE.^{101,102}

In addition, the long-term, effective treatment of patients with AE may have a beneficial effect also on respiratory symptoms, and serum IgE.¹⁰³ In adults, long-term treatment with 0.1% tacrolimus ointment appears to be at least as effective as a corticosteroid regimen for the trunk and extremities, and more effective in the face and neck area. Both topical tacrolimus and corticosteroids increase skin recall activity, and decrease serum IgE in patients with good treatment response. Taken together, these results suggest that skin inflammation in AE should be treated effectively, which could lead to an improvement in the Th1/Th2 balance in the skin, and to long-term improvement in the severity of the AE.^{103,104}

These drugs are recommended for use as second-line therapy for the short-term and non-continuous treatment of AE in patients who do not respond adequately to topical corticosteroids or in

whom they are contraindicated. According to the latest knowledge, there is no scientific evidence of an increased risk for malignancy due to a topical treatment with calcineurin inhibitors.^{94a}

Recommendations

TCI are important anti-inflammatory drugs to be used in AE (–, D).

TCI have a significant effect compared to placebo in short-term and long-term treatment of AE (1b, A).

TCIs are especially indicated in problem areas (face, intertriginous sites, anogenital area; 1b, A).

Proactive therapy with twice weekly application of tacrolimus ointment may reduce relapses (1b, A).

Effective sun protection should be recommended in patients treated with TCI (–, D).

Antipruritic therapy

Itch is the most important clinical symptom in AE, with peculiar impact on emotional dimensions of perception as compared to other pruritic dermatoses like urticaria. Concerning pruritus accompanying AE, few studies investigate the antipruritic effect only. In most studies, pruritus is part of the total symptom score using the EASI and SCORAD. For example, topical and systemic corticosteroids, TCI, cyclosporine and UV-irradiation have significant influence on pruritus while only single studies specifically investigate the relief of pruritus intensity (Table 3).

Table 3 Antipruritic therapies in AE. Recommendation for topical and systematical therapies based on clinical trials and expert opinion

| Therapeutical modalities | Examples |
|--|---|
| General principles | Emollients/basis therapy to reduce dry skin Elimination of provocative factors: avoidance of too long and hot bathing, contact with irritant substances or allergens |
| Unspecific physical modalities | Acupuncture Cutaneous field stimulation |
| Anti-inflammatory therapy | Corticosteroids, t* Ciclosporine, o* Tacrolimus, t* Pimecrolimus, t* Ultraviolet light (NB-UVB) |
| Adjuvant specific antipruritic therapies | Creams/lotions containing urea, camphor, menthol, polidocanol or N-palmitoylethanolamin, t Capsaicin, t Opioid receptor antagonists, o* (e.g. naltrexone) |
| Sedation | Sedative antihistamines, o* |

AE, atopic eczema; t, topically; o, orally.

*As proven by randomized, controlled trials.

Antipruritic therapy in AE is multidimensional treating the symptom itself, the contributing factors such as dry skin, inflammation and the related scratch lesions. Therefore, several general measures can be recommended (see 'Basic treatment'). Based on expert opinion, short-term relief of pruritus can be achieved by topicals containing urea, camphor or menthol preparations as well as wet, cooling or fat-moist wrappings,⁶¹ wrappings with black tea, short and lukewarm showers. Unspecific physical modalities are described to be beneficial like acupuncture,¹⁰⁵ and cutaneous field stimulation.¹⁰⁶

Anti-inflammatory therapies acting on pruritus

Glucocorticosteroids Several studies describe the anti-inflammatory effect of topical corticosteroids in AE, in which pruritus was one parameter among others such as erythema, induration, scaling and excoriation (see chapter Topical Anti-inflammatory Therapy). In sum, these studies suggest that topical corticosteroids have a rapid antipruritic effect and can also be used in 'proactive' therapy.¹⁰⁷ No study focuses solely on the onset, mechanisms and duration of the pruritus relief in AE. However, it seems likely that the anti-inflammatory effect of glucocorticosteroids is responsible to partly abolish pruritus.¹⁰⁸ This also holds true for systemic glucocorticosteroids, for which no specific studies on an anti-itch effect in AE were published.

Recommendations

There is evidence that topical corticosteroids can be used in the initial phase of AE exacerbation to control pruritus (1b, A).

Interferon (IFN) gamma Interferon gamma appears to have a beneficial effect on pruritus in AE.¹⁰⁹ In a double-blind study, pruritus was reduced by 50% even 1–2 years after long-term treatment with recombinant human interferon gamma.¹¹⁰

Recommendations

There is evidence that systemic IFN gamma influences AE itch, however, therapeutical use was not further investigated following initial trials (2b, B).

Calcineurin inhibitors Topical calcineurin inhibitors relieve significantly pruritus in AE. Itch is completely relieved after the first days of treatment in adults and children. Studies report of relief even 3 days of topical application of tacrolimus^{111,112} and pimecrolimus.^{113,114}

Recommendations

There is evidence that TCI can be used in AE until clearance of eczema to control pruritus (1b, A).

UV therapy UV irradiation relieves pruritus in AE demonstrated in a study that compared UVB to placebo treatment.¹¹⁵ Also a

study proved that Narrowband-UVB was more effective than UVA¹¹⁶ and UVA1.¹¹⁷

Recommendations

There is evidence that UV-therapy can be used in AE to relieve pruritus. Narrow band UVB seems to be most preferable (2b, B).

Cyclosporine A See 'Systemic Immunosuppression' (Part II).

Intravenous Immunoglobulin therapy See 'Systemic Immunosuppression'.

Mycophenolat mofetil See 'Systemic Immunosuppression'.

Specific antipruritic therapies

Topical anaesthetics Local anaesthetics such as benzocaine, lidocaine, polidocanol as well as a mixture of prilocaine and lidocaine are widely used as short-term effective topical antipruritics. In experimental studies, the antipruritic effect of local anaesthetics was demonstrated in AE¹¹⁸ but controlled clinical trials investigating the antipruritic effects of local anaesthetics in AE are pending. Case series described the efficacy of a combination of polidocanol and 5% urea.¹¹⁹ In children with AE, the combination showed a pruritus improvement of 30% in comparison with an emollient.¹²⁰ None of these substances is licenced for AE in Europe.

Recommendations

Although there is evidence that short-term application of topical local anaesthetics may reduce itch sensation in AE (4, C), routine clinical use in AE cannot be recommended as an adjuvant antipruritic therapy in AE. (4, C)

Cannabinoid receptor agonist Topical cannabinoid receptor agonists have been described to exhibit antipruritic and analgesic properties. Experimentally induced pain, itch and erythema could be reduced by application of a topical cannabinoid agonist.¹²¹ One cosmetic product containing the cannabinoid agonist *N*-palmitoylethanolamin was used in a multicentric, large cohort, open label study as adjuvant treatment in AE.²⁵ 2456 patients including over 900 children applied the cream twice daily. Pruritus and the need to use corticosteroids were reduced up to 60%.

Recommendations

There is preliminary evidence that topical *N*-palmitoylethanolamin may be effective as an adjuvant antipruritic therapy in AE, but further trials are needed before an evidence based recommendation can be given (4, B).

Capsaicin Capsaicin, a naturally occurring alkaloid and the principal pungent of hot chilli peppers, has been advocated to be antipruritic in various dermatoses. Repeated topical application of

capsaicin releases and prevents specifically the reaccumulation of neuropeptides in unmyelinated, polymodal C-type cutaneous nerves. Capsaicin exerts its functions via binding to a capsaicin-specific receptor, i.e. the transient receptor potential channel vanilloid (TRPV1) which is located on free nerve endings. Concerning AE, experimental studies¹²² and case series¹²³ report on clear itch reduction. No controlled study was performed as of yet.

Recommendations

There is preliminary evidence that capsaicin is useful in the treatment of AE itch but further trials are needed before an evidence based recommendation can be given (4, B).

Topical doxepin Five percent doxepin cream exhibited antipruritic effects in controlled studies in AE.¹²⁴ However, topical doxepin therapy is not licenced and not used in any European country due to an increased risk of contact allergy, especially when the treatment exceeds 8 days.

Recommendations

At the moment there is not enough RCT evidence to support the use of doxepin in the treatment of AE itch (2b, B).

Topical mast cell stabilizers Mast cell mediators such as tryptase and histamine contribute to induction of pruritus in AE. Accordingly, the application of mast cell degranulation inhibitors or stabilizers seems reasonable. However, in a multicenter, double-blind, placebo-controlled trial applying 3% hydrogel formulation of tiacrilast (mast cell inhibitor) against vehicle in atopic dermatitis, there was no significant improvement of pruritus.¹²⁵ In another study, pruritus in children with AE responded to topical sodium cromoglycate,¹²⁶ which was proven by a recent placebo-controlled study.¹²⁷

Recommendations

At the moment there is not enough RCT evidence to support the use of mast cell stabilizers in the treatment of AE itch (2b, B).

Leukotriene receptor antagonists Preliminary studies showed reduction of pruritus in patients with AE during treatment with the leukotriene receptor antagonists zafirlukast and zileuton.^{128–130} However, due to a high rate of side-effects the substances were not developed to regular therapies of AE.

Recommendations

At the moment there is not enough RCT evidence to support the safe use of leukotriene receptor antagonists in the treatment of AE itch (2b, B).

Opioid receptor antagonists naltrexone and nalmefene The mu-opioid receptor antagonist nalmefene was applied in controlled,

randomized studies in AE. A dosage of 10 and 20 mg each once per day showed significant relief of pruritus in three studies.^{131–133} In open label trials and one double-blind, placebo-controlled study trial, the only orally active mu-opioid antagonist naltrexone 25–150 mg per day showed considerable antipruritic effects.^{134,135} None of these substances is currently licenced for treatment of AE itch.

Recommendations

Although there is evidence that opioid receptor antagonists naltrexone and nalmefene may reduce AE itch (1b, A), there is insufficient data to recommend routine use of these substances in AE. (–, D)

Selective serotonin reuptake inhibitors The antipruritic effect of the selective serotonin reuptake inhibitor paroxetine and fluvoxamin was investigated in an open label trial in dermatological patients. Single patients with pruritus due to AE were included which responded with considerable reduction of pruritus. In these patients, the pruritus was reduced about half of intensity (maximal antipruritic effect score, $45.0 \pm 7.1\%$).¹³⁶

Recommendations

At the moment there is not enough RCT evidence to support the use of selective serotonin reuptake inhibitors paroxetine and fluvoxamine in the treatment of AE itch (4, C).

Antihistamines

Antihistamines have been used for decades, in an attempt to relieve pruritus in patients with AE. However, only a few randomized controlled trials have been conducted and they have in the majority shown only a weak or no effect in decreasing pruritus.^{137–142}

The first generation of sedative antihistamines, such as hydroxyzine, clemastine fumarate and dimetinden maleate, may allow a better sleep pattern in acute situations with exacerbations of eczema (evidence level D). Concerning the newer non-sedating antihistamines, single studies using loratadine, ceterizine or fexofenadine demonstrated no or only a weak relief of pruritus in AE.^{143–145} A significant, but clinically small, antipruritic effect of fexofenadine 60 mg twice daily has been described.¹⁰⁸ An effect on itch of a high dosage of 20–40 mg ceterizine daily has been observed, but this effect was primarily attributed to sedation.¹⁴⁴

Diepgen *et al.*¹⁴⁶ reported in infants with severe AE a corticosteroid sparing effect of ceterizine and judged this as an indirect measure for the efficacy of ceterizine on pruritus. Murata *et al.*¹⁴⁷ compared in patients with pruritic diseases (including eczema cases) effects of sedating and non-sedating antihistamines: similar effects on itch intensity were seen, but only non-sedating antihistamines reduced significantly the impairment in work productivity and daily activity.

In general, antihistamines are safe to use, also for a long period of time,¹⁴⁸ and the major advantage seems to be relief of the symp-

toms of co-morbidities such as allergic asthma, rhino-conjunctivitis, urticarial dermatographism and urticaria. Topical antihistamines have no effect on itch beyond that of their cooling vehicles.

Summary of evidence-based data:

There are limited data for the antipruritic effect of antihistamines (H1-antagonists) in AE, and the effect of both first and second generation antihistamines on pruritus, in patients suffering from AE, is very limited.

Recommendations

There is not enough evidence to support the general use of both first and second generation antihistamines (H1-antagonists) for treatment of pruritus in AE (1b, A).

Antimicrobial therapy

A number of defects in innate cutaneous immunology may explain the high rate of cutaneous colonization with *Staphylococcus aureus* (up to 90% in moderate to severe eczema) in AE.^{149,150} There is evidence for an association of *S. aureus*-derived exotoxins including superantigens and pore forming haemolysins with disease exacerbation,^{151–153} reviewed by De Benedetto *et al.*¹⁴⁹ and Niebuhr and Werfel¹⁵⁰ supporting early observations that the density of *S. aureus* colonization in AE is significantly correlated with clinical severity,¹⁵⁴ and that patients with severe AE may improve (but not be cured) by antistaphylococcal treatment.¹⁵⁵ In severe exacerbations systemic antibiotic treatment may be helpful.

In general, improving eczema with anti-inflammatory regimen (i.e. TCS, TCI and UV) decreases staphylococcal colonization. This led to the clinical concept that patients with high numbers of colonizing *S. aureus* can benefit from combination treatment with corticosteroids and antimicrobial treatment, in most cases using topical antiseptics like triclosan, chlorhexidine or crystal violet 0.3%.^{156,157} In addition, a combination of sodium hypochlorite in baths with antibiotics has recently been published to have minor to moderate effects on eczema in children with AE.¹³ However, formal evidence on beneficial effects of topical antiseptics coming from prospective controlled studies is still not available. A recent Cochrane review did not find any benefit for antibacterial soaps (1 trial, 50 participants), or antibacterial bath additives (2 trials, 41 participants), or topical antibiotics/antiseptics (4 studies, 95 participants).¹⁵⁸

Apart from specific indications such as overt secondary infection or presence of beta-hemolytic streptococci^{159,160} or from visual superinfections of the skin with *S. aureus*, treatment of eczema with antibiotics had no effect in regards to clinical improvement and sparing of steroids¹⁶¹ and should therefore not be performed. Besides being not effective on the severity of eczema, antibiotic eradication of *S. aureus* as a long-term strategy bears the risk of increasing prevalence of antibiotic resistance.^{162,163} Particularly, topical antibiotics should not be used for longer periods in the treatment of AE.

The use of silver-coated textiles and silk fabric with the durable antimicrobial finish AEGIS ADM 5772/S can reduce *S. aureus* colonization and eczema severity.^{164–166} These newer options are still under investigation. Of note, there is some concern about the safety of silver-coated textiles in infants and toddlers.

Secondary infections with yeasts, dermatophytes or streptococcal infections have also been implicated as trigger factors in AE.¹⁶⁷ Intense erythema in skin folds of children with a flare of AE may warrant a search for streptococcal skin infection. In general, signs of secondary infections should be treated if present. Antimicrobials are proposed for the treatment of 'head and neck' variant of AE, often associated with *Malassezia sympodialis* superinfection (recently reviewed by Darabi *et al.*¹⁶⁸ Systemic ketoconazole¹⁶⁹ and topical ciclopiroxolamine¹⁷⁰ have been shown to improve eczema significantly within 4 weeks in placebo-controlled trials in patients with 'head-neck-shoulder dermatitis'. Instead of ketoconazole, other imidazole derivatives (fluconazole or itraconazole) are proposed nowadays due to a better benefit : side effect ratio.

Viral infections are occurring more frequently in AE patients than in normal individuals, with a tendency to disseminated, widespread disease and named after the causative virus as eczema molluscum, eczema vaccinatum or EH.²⁰ EH has been described following corticosteroid and calcineurin inhibitor therapy, but recent data indicate that patients with severe, untreated AE, a high total serum-IgE and early onset of AE are at risk for EH, whereas pretreatment with topical corticosteroids does not imply a risk.¹⁷¹ The mainstay of EH therapy is prompt systemic antiviral chemotherapy with i.v. aciclovir, but a number of alternative treatment modalities exist.¹⁷¹

Recommendations

Oral antibiotics have no benefit on the skin condition in AE as long as skin lesions are not obviously superinfected (1b, A).

A short-term treatment with systemic antibiotics may be beneficial if the skin is obviously superinfected with bacteria (2b, B).

There is evidence from open observational studies only that antiseptic substances are beneficial for the treatment of AE (4, C).

An antimycotic therapy may be efficient in AE patients suffering from the 'head and neck' variant (2b, B).

Topical glucocorticosteroids or calcineurin inhibitors reduce the colonization rate of *Staphylococcus aureus* in AE (4, C).

Antiseptic textiles have a moderate clinical effect on AE (2b, B).

The long-term application of topical antibiotics is not recommended due to the risk of increasing resistances and sensitizations (the latter being relevant for a subgroup of topical antibiotics only; -, D).

EH should be treated without delay using systemic antiviral therapy, such as systemic aciclovir (4, D).

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