European Dermatology Forum

EDF-Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis) Part I

Developed by the Guideline Subcommittee "Atopic Eczema" of the
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Consensus based European Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis) in Adults and Children
Part I

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Declaration of Conflict of Interest

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Table R1 (online repository)

Assignment of guideline sections to draft authors

Part I

Introduction	(Andreas Wollenberg & Johannes Ring)
Method of guideline formation	(Andreas Wollenberg & Johannes Ring)
Patient perspective	(Antje Fink-Wagner, patient representative)
General measures and avoidance strategies	(Susanne Lau & Thomas Werfel)
Basic emollient treatment and bathing	(Jacek Szepietowski & Alain Taieb)
Dietary intervention	(Antonella Muraro & Johannes Ring)
Topical anti-inflammatory therapy	(Thomas Bieber & Giampiero Girolomoni)
Phototherapy	(Alain Taieb & Magda Operacz)
Antipruritic therapy	(Jacek Szepietowski & Uwe Gieler)

Part II

Antimicrobial therapy	(Peter Schmid-Grendelmeier & Stephanie Christen-Zäch)
Systemic anti-inflammatory treatment	(Mette Deleuran & Andreas Wollenberg)
Other systemic treatment	(Dagmar Simon & Antonio Torrelo)
Allergen specific immunotherapy	(Magda Operacz & Johannes Ring)
Complementary medicine	(Torsten Schaefer & Johannes Ring)
Psychosomatic counselling	(Uwe Gieler & Zsuzsanna Szalai)
Educational interventions	(Zsuzsanna Szalai & Sebastien Barbarot)
Conclusion and future options	(Andreas Wollenberg & Johannes Ring)

Table R2: Members of the guideline panels (role in the guidelines development, discipline, institution)

Name	Role in the guideline development, discipline / content expertise, institution / geographic location	Institutions represented
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List of Abbreviations

AAD	American Academy of Dermatology
AD	Atopic dermatitis
AE	Atopic eczema
AEGIS	3-trimethylsilylpropyl-dimethyloctadecyl ammonium chloride
AH	Antihistamines
AGREE	Appraisal of Guidelines Research and Evaluation
APT	Atopy patch test
ASIT	Allergen-specific Immunotherapy
AZA	Azathioprine
BB-UVB	Broadband ultraviolet B
BCC	Basal Cell Carcinoma
BO	Borage oil
CAM	Complementary alternative medicine
CAP-FEIA	CAP Fluorescence Immunoassay
CHM	Chinese herbal medicine
DBPC	Double-blind placebo-controlled
DBPCFC	Double-blind placebo-controlled food challenge
DHA	Docosahexaenoic acid
EADV	European Academy of Dermatology and Venereology
EASI	Eczema Area and Severity Score, a signs score
EAT	Enquiring About Tolerance
EC	Eczema coxsackium
EC-MPS	Enteric-coated mycophenolate sodium
EDF	European Dermatology Forum
EFA	European Federation of Allergy and Airways Diseases Patients' Associations
EH	Eczema herpeticum
EPO	Evening primrose oil
ETFAD	European Task Force on Atopic Dermatitis
EU	European Union
EV	Eczema vaccinatum
FA	Food allergy
FTU	Fingertip unit
GAAPP	Global Allergy and Asthma Patient Platform
HBD	Human-ß-defensin
HDM	House Dust Mite
HTA	Health Technology Assessment
H1R	Histamin 1 receptor
IA	Immunoadsorption
ICAM1	Intercellular Adhesion Molecule 1
IGA	Investigators Global Assessment, a signs score
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukin
IVIG	Intravenous immunoglobulins
IFN-α	Interferon alpha
IFN-γ	Interferon gamma

JAK	Janus kinase
LEAP	Learning Early About Peanut Allergy
LTC4	Leukotriene C4
LTD4	Leukotriene D4
LTE4	Leukotriene E4
MCV	Molluscum contagiosum virus
MMF	Mycophenolat Mofetil
MTX	Methotrexate
mTLSS	modified Total Lesion Symptom Score
NB-UVB	Narrow band Ultraviolet B
OFC	Oral food challenge
OTC	Over the counter
PDE 4	Phosphodiesterase 4
PE	Patient education
PO-SCORAD	Patient-oriented Scoring of Atopic Dermatitis
PUVA	Psoralen and ultraviolet A
RCT	Randomized controlled trial
ROS	Reactive oxygen species
SASSAD	Six Area Six Signs Atopic Dermatitis score
SCC	Squamous Cell Carcinoma
SCIT	Subcutaneous Immunotherapy
SCORAD	Scoring of Atopic Dermatitis, a composite score
SLIT	Sublingual Immunotherapy
SPT	Skin prick test
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TPMT	Thiopurine methyltransferase
TSH	Thyroid-stimulating hormone
Th1	T helper 1 cells
Th2	T helper 2 cells
Th17	T helper 17 cells
UV-light	Ultraviolet light
VOCs	Volatile organic compounds
VZV	Varicella-zoster Virus
QoL	Quality of life
TSLP	Thymic stromal lymphopoietin

Abstract

This guideline was developed as a joint interdisciplinary European project, including physicians from all relevant disciplines as well as patients. It is a consensus based guideline, taking available evidence from other guidelines, systematic reviews, and published studies in to account.

This first part of the guideline covers methods, patient perspective, general measures and avoidance strategies, basic emollient treatment and bathing, dietary intervention, topical anti-inflammatory therapy, phototherapy and antipruritic therapy, whereas the second part covers antimicrobial therapy, systemic treatment, allergen specific immunotherapy, complementary medicine, psychosomatic counselling and educational interventions.

Management of AE must consider the individual clinical variability of the disease, highly standardized treatment rules are not recommended. Basic therapy is focused on treatment of disturbed barrier function by hydrating and lubricating topical treatment, besides further avoidance of specific and unspecific provocation factors. Topical anti-inflammatory treatment based on glucocorticosteroids and calcineurin inhibitors is used for flare management and for proactive therapy for long term control. Topical corticosteroids remain the mainstay of therapy, whereas tacrolimus and pimecrolimus are preferred in sensitive skin areas and for long term use. Topical phosphodiesterase inhibitors may be a treatment alternative when available. Adjuvant therapy includes UV irradiation, preferably with UVB 311 nm or UVA1. Pruritus is targeted with the majority of the recommended therapies, but some patients may need additional antipruritic therapy. Antimicrobial therapy, systemic anti-inflammatory treatment, immunotherapy, complementary medicine and educational intervention will be addressed in part II of the guideline.

Key words: Atopic eczema, atopic dermatitis, pruritus, immunomodulation, emollients

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Introduction

Atopic eczema (AE; atopic dermatitis, eczema, “Neurodermitis” in German speaking countries, endogenous eczema, neurodermatitis) is an inflammatory, pruritic, chronic or chronically relapsing skin disease occurring often in families with other atopic diseases (bronchial asthma and/ or allergic rhinoconjunctivitis). AE is one of the most common non-communicable skin diseases which affects up to 20% of children and 2-8% of adults in most countries of the world. In many instances AE begins in childhood, while severe cases may persist in adulthood. About one third of adult cases develop in adulthood. AE is often the first step in the development of other atopic diseases, such as allergic rhinoconjunctivitis or asthma and food allergy (FA).

Though several diagnostic criteria have been proposed over time, the classical Hanifin & Rajka criteria are still the most widely used criteria worldwide (1). There is no pathognomonic laboratory biomarker for diagnosis of AE. The most typical feature, the elevation of total or allergen-specific IgE levels in serum or the detection of IgE-mediated sensitization in skin tests, is not present in all individuals suffering from AE; the term “intrinsic” (non-IgE-associated) AE has been introduced to distinguish the latter group from “extrinsic” (IgE-associated) forms of AE (2). The controversy in terminology is going on until today, and has practical implications regarding avoidance strategies for AE management.

Apart from a strong genetic influence (80% concordance in monozygous twins, 20% in heterozygous twins), there are other characteristic features in pathophysiology. These include an immune deviation towards the T helper 2 (Th2) pathway in the initiation phase with consequent increased IgE production; an increased production of mediators from various inflammatory cells, a deficient skin barrier function (“dry” skin) due to abnormal lipid metabolism and epidermal structural protein formation of filaggrin and protease inhibitors; an abnormal microbial colonization with pathogenic organisms such as Staphylococcus aureus or Malassezia sp. (compared to Staphylococcus epidermidis in normal individuals) and subsequently increased susceptibility to skin infection; and an obvious, strong psychosomatic influence.

After establishing the diagnosis of AE, the overall disease severity must be determined by evaluating both objective signs and subjective symptoms. As signs-only scores are lacking the subjective part of pruritus and sleep disturbance, composite scores assessing signs and symptoms must be used to assess overall disease severity (3). The classical composite score is the “Scoring of Atopic Dermatitis” (SCORAD) developed by the European Task Force of Atopic Dermatitis (ETFAD) (4). AE with a SCORAD above 50 is regarded as severe, while SCORAD values below 25 are considered as mild AE (3, 5). The Patient-oriented SCORAD (PO-SCORAD) is a tool for assessing AE severity independent of the physician, and the results correlate well with SCORAD (6). In contrast, the Eczema Area and Severity Score (EASI) is a signs-only score assessing visible lesions only, but not the subjective symptoms. The Patient-Oriented Eczema Measures for Eczema (POEM) are a symptoms-only score to measure subjective symptoms, but not objective signs in clinical trials. The Investigators Global Assessment (IGA) is frequently used, but more a global assessment than a validated score. In contrast to SCORAD, POEM and EASI, it is a based on a single

global assessment by the investigator only. The HOME group is an initiative of methodologists, industry representatives and physicians interested in outcome measures for AE, which has done considerable work in recommending instruments for measurement of the previously identified domains of AE such as signs, symptoms, quality of life and long term control (7).

Most AE cases can be regarded as mild, whereas less than 10% of patients suffer from severe eczematous skin lesions. This percentage of severe cases seems to be higher in the adult AE population (8). This guideline covers most of the important and relevant strategies for management of AE.

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. This is a consensus-based S2k guideline, though it has an additional strong focus on evidence from the literature. Consensus was achieved among the nominated members of the European interdisciplinary expert group.

Base of the guideline

This is an update of the 2012 guideline on atopic dermatitis (8, 9). The former, first version of this guideline had been based on the evidence-based national guideline from Germany (10), the HTA report (11), as well as the position paper of the ETFAD (12), which were compared and assessed. The former committee had decided that all these documents fulfilled enough criteria to be used as the base of the first version of the European Guidelines on Treatment of Atopic Eczema (8, 9).

Data base and literature search

For this consensus-based guideline, no systematic literature review has been performed. During the kick-off meeting in Copenhagen in 2015, subgroups of two authors were determined among the expert panel to be responsible for the draft of specific sections of the guideline by virtue of their clinical and scientific expertise (Table R1). Discrepancies between the two respective authors were escalated to the steering committee. The subgroups were in charge of the search for best available evidence, the summary thereof and of critically appraising the evidence to inform the drafted recommendations. Specific inclusion or exclusion criteria for the selection of the evidence (such as the limitation to a certain study design) were not defined and the authors were encouraged to include the ‘best available evidence’.

Data were included only, if a reference had been published as a full paper in a peer reviewed journal by March 2017, but not based on an abstract or a conference presentation only.

Classification of presented studies with regard to study type

To give the reader a general impression of the quality of the evidence presented in this guideline, grades of evidence were assigned using the system employed in the 2012 version of the guideline (table 1) (8, 9). These need to be interpreted with caution, however, as the literature search that was undertaken followed a targeted rather than systematic approach.

Recommendation levels (table 2) were given only for those therapies available in Europe by September 2017, though the label did not have to specifically include AE as a licensed indication. Therapies not available in Europe by September 2017 could be mentioned in the manuscript, but no formal therapeutic recommendation would be given for these. High level evidence with a potential to significantly change current treatment paradigms published after

these deadlines could be included upon vote during the final meeting of the guideline committee in Geneva in 2017.

The expert panel tried to use standardized language for the recommendations given, but would prefer a consensus vote on non-standardized language over standardized language, if the highly variable clinical presentation of AE would suggest that a non-standardized wording be more useful in clinical reality from a patient's or physicians perspective (see table 3 for standardized wording of recommendations).

Consensus process

The committee designated all recommendation statements, as well as some especially important areas as those requiring consensus. Consensus conferences were held in Copenhagen in October 2015, in Vienna in September 2016 and in Geneva in September 2017. Johannes Ring acted as the moderator during all face-to-face meetings.

All sections with recommendations were discussed within the whole group and consensus was defined as approval by at least 75 % of the panel members. All consented recommendations are marked with grey boxes.

External review

According to the EDF standard operation procedure, all EDF members 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 three years, but advances in medical sciences may demand an earlier update.

Target group

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

AE management from a patient's perspective

Due to the variety of different AE therapies and different individual reactions, patients and their caregivers need clear and easy to understand strategies for their individual needs in therapy, and in order to become comfortable to take over responsibility for the treatment of their chronic condition. Patients and caregivers need to be trained to understand and apply the existing therapeutic options and best disease management immediately after a diagnosis of AE. Health Care Professionals need to be reimbursed for education, as the training of patients and caregivers is an imperative prerequisite for the essential concordance between the patient and the treating physician. Free access to care and medication is essential from a patient's perspective. A multidisciplinary approach including psychological advice is needed to overcome the painful, itching and stigmatizing flare-ups and their impact on quality of life. Rehabilitation may play a key role.

Patients and caregivers should be able to identify their individual symptoms, become aware of the need and benefit of sufficient amounts of basic management (topical treatment, avoidance of specific and unspecific trigger factors) and to understand certain needs of anti-inflammatory treatment based on topical glucocorticosteroids (TCS) and topical calcineurin inhibitors (TCI). This will lead to a fast and effective short-term management of exacerbations, as well as long term control by proactive therapy. Movement of patients and caregivers towards unapproved complementary alternative medicine (CAM) and non-compliance often result in worsening of the disease and should be avoided.

Cases of severe AE should be discussed openly and in detail between the treating physician or multidisciplinary team and the patient or caregiver, since many patients cannot overlook the therapeutic options, even if they have access to transparent guidelines. Patients and caregivers should actively be involved in therapeutic decisions at all stages in order to achieve therapeutic success.

Patients with a not well controlled AE should be informed about new therapeutic options and possible side effects. Guidelines for patients and caregivers should be in place.

General measures and avoidance strategies

The identification of individual trigger factors is crucial in the management of AE and their avoidance allows longer phases of remission or total clearance of symptoms. It is important to differentiate between the genetic predisposition towards hypersensitive, dry skin with barrier dysfunction – largely corresponding to ichthyosis vulgaris – which cannot be "cured" and the inflammatory skin lesions which can very well be treated and disappear.

In avoidance recommendations, one must distinguish between primary, secondary and tertiary prevention measures. Among provocation factors, specific and non-specific elicitors must 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, water) or biological (allergens, microbes) in nature. Information on unspecific irritants and their role in aggravating AE 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, “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 must be mentioned. There is evidence from epidemiological trials that exposure to indoor chemicals, such as formaldehyde, increases skin barrier disturbance (13); a mixture of volatile organic compounds has been shown to increase the intensity of atopy patch test reactions to aero-allergens in patients with AE (14).

Exposure to traffic exhaust has been shown to be associated with an increased risk to develop AE in pre-school children (15, 16). Moreover, diesel exhaust particles may favor alloknesis and skin scratching, and thus worsen AE (17).

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 (18). The prevalence of smoking was higher in severe AE, as shown in a recent cross sectional study investigating the entire Danish population (19). A systematic review of 86 studies confirmed the association of smoking and AE in adolescents and adults in all continents of the earth (20). It remains unclear, however, if smoking is a provocation factor in AE or if the burden of AE leads to more frequent smoking habits (20).

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 atopic diseases in Germany (21).

Specific allergen avoidance

Aeroallergens

Aeroallergens can elicit eczematous skin lesions in sensitized patients with AE, which can be explained by increased permeability of the skin for inhalant allergens in patients with skin barrier defects (22). Positive atopy patch tests are associated with specific IgE and positive histories of flare-ups of AE to seasonal allergens (23).

Many airborne allergens eliciting AE are derived from house dust mites (HDM) of the species *Dermatophagoides pteronyssinus* and *D. farinae*. The enzymatic activity of major mite allergens is found to destroy tight junctions of the epithelial cells in the bronchial mucosa and may thus also deteriorate the skin barrier dysfunction in patients with AE (24).

House dust mites are living in a complex eco-system consisting of air humidity, temperature and presence of 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 allergens present in settled and airborne dust indoors. Encasings of mattresses and beddings protect humans from house dust mites in mattresses. There are also mite-proof pyjamas ("eczema overalls"). Some studies are showing a clear-cut benefit from house dust mite avoidance strategies in the improvement of AE (25, 26). A recent meta-analysis was not in favor of house dust mite avoidance in established AE (27). Rehabilitation programs in mite-free environments – like in alpine climate – have shown to lead to significant and long-lasting improvement of AE (28).

Pollen in the outdoor air also can elicit flares of AE as has been shown in a nested case control study in pre-school children (29). A challenge of sensitized patients with grass pollen in a challenge chamber led to exacerbation of AE in winter in a proof-of-concept study (30). 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 aware that contact with animals may lead to a deterioration of skin symptoms. While 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 (31, 32). There is no evidence that dogs increase the risk of AE in children; recent studies suggest that dogs might even protect from AE, possibly due to exposure to non-pathogenic microbes (33-35). Once a patient is sensitized to a pet and shows symptoms after contact, avoidance is necessary.

Furthermore, the exposure towards bacteria is increased if dogs live in a household, which may have a protective effect in terms of primary prevention and immune regulation. However, if AE has developed, there may be a risk of bacterial superinfection if skin lesions are present and dogs have a close contact to the patient (36). Staphylococcus aureus, which heavily colonizes the lesions of AE, produces extracellular proteases, which cause barrier breakdown in the skin and thus facilitate the uptake of allergens and specific sensitization.

Dietary Recommendations

See chapter "Dietary intervention"

Vaccinations

It is a common misconception that AE patients and especially children diagnosed with AE should avoid routine vaccinations. There is no evidence, that recommended vaccinations in infancy and early childhood have an impact on the development of AE or other atopic diseases (37). All children diagnosed with AE should be vaccinated according to the local or national vaccination plan. Vaccinations should not be administered during acute flares – in those cases two weeks of well-conducted TCS therapy followed by a normal vaccination procedure are recommended (37). Patients on immunosuppressive therapy with cyclosporine or related drugs should consult a specialist before live vaccination is performed (37). The only exception from this rule has been the intracutaneous smallpox vaccination with an attenuated live vaccine, which is contraindicated in AE patients due to risk of life-threatening eczema vaccinatum (38). A safe and effective alternative regimen with a highly attenuated MVA vaccine may circumvent these problems for AE patients in the future (39).

Clothing and textiles - contact allergens

Smooth clothing and avoidance of irritating fabrics and fibers is essential in the avoidance of primary skin irritation. Silk garments with an AEGIS-coating are lightweight and comfortable to wear, but do not improve eczema severity over standard of care treatment (40). Too occlusive clothing inducing heat sensations should be avoided.

Obviously, contact allergens relevant to the patient should also be avoided. This is of special relevance if type IV allergy to ingredients of emollients has been diagnosed by classical patch tests. Emulsifiers, fragrances and preservatives are the main cause of contact allergy to cosmetics (41).

Occupational aspects

Special recommendations must be given in individual counseling programs regarding the choice of profession. There is common consensus that occupations involving contact with strongly sensitizing substances should be avoided by patients with AE (42). Professions with skin irritating tasks are not recommended to atopic individuals with a history of persistent or relapsing hand eczema. The risk of contact sensitization is slightly increased in patients with AE (43).

Summary of evidence

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 therefore

improve AE. The latter is controversial, since a recent meta-analysis would not confirm this effect. (2b)

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

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

In spring and summertime pollen exposure may exacerbate AE in the air-exposed skin areas. (-)

Vaccination does neither improve nor worsen the natural course of AE (2a).

Recommendations

Pollen avoidance measures can be recommended during the pollen season. (-, D)

House dust mite avoidance measures may be tried in selected cases. (-, D)

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

All children diagnosed with AE should be vaccinated according to the national vaccination plan (2a, B).

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

Emollient therapy and skin care

Dry skin is one of the characteristic symptoms of AE. 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 (44). 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 (45).

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 (3). A further cleansing followed by a rapid rinse is performed in the bath (27-30°C). The short duration of the bath (only 5 minutes) and the use of bath oils (2 last minutes 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 (see next section on emollient therapy).

Adding antiseptics such as sodium hypochlorite to the bath-water is an additional option for treatment of AE because of its bacterial count inhibiting activities (46, 47). A study showed that children bathing in 0,005% bleach experienced an improvement of their AE (47, 48). In a recent study sodium hypochlorite baths did not show superiority to water baths concerning the severity of AE, but allowed a reduction in topical corticosteroid and antibiotic usage (49). Salt baths may be beneficial because of removing the dead keratin material (50). Salt baths are useful especially in heavily impetiginized or ichthyotic skin. A recent study suggested usage of fragrance-free baby oil as a soap substitute, especially in populations where specially designed emollients are not affordable (51).

Bath oils are a valuable addition for skin care especially in babies and children. Bath additives containing potentially allergenic proteins such as from peanut or colloidal oat should be avoided in the most vulnerable age group before the age of 2 (3) It should be emphasized that most bath oils commercially available in Europe are practically free of these protein allergens.

Recommendations

Adding antiseptics such as sodium hypochlorite to the bath-water may be useful for treatment of AE (1b, A).

Emollient therapy

By tradition, emollients are defined as topical treatment with vehicle-type-substances lacking active ingredients. These emollients are extremely helpful for AE patients, and contain usually a humectant (promoting stratum corneum hydration, such as urea or glycerol) and an occludent (reducing evaporation, such as petrolatum). Recently, marketing of non-medicated “emollients” containing active ingredients have softened the delineation of emollients from topical drugs. Throughout this guideline, “emollients” are defined as “topical formulations with vehicle-type-substances lacking active ingredients”, whereas “emollients plus” refers to “topical formulations with vehicle-type substances and additional active, non-medicated substances”.

The direct sole use of emollients on inflamed skin is poorly tolerated and it is better to treat the acute flare first. Emollients are the mainstay of management. Hydration of the skin is usually maintained by at least twice daily application of moisturizers with a hydrophilic base, e.g. 5% urea (52). According to the acuity of the skin condition, lipophilic bases are also helpful. 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 for e.g. Finland and Switzerland, where prescription and reimbursement are usual) and the quantities required are usually high (up to 100 g per week in young children, and up to even 500 g in adults). The use of pure oil products such as coconut oil instead of emulsions will dry out the skin, increase the transepidermal water loss and is therefore not recommended.

The applied amount of topicals may also follow the fingertip unit rule: A fingertip unit (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 (53).

A better molecular and biochemical knowledge of the skin in AE should provide access to barrier improving topical agents. There is increasing evidence-based proof for the use of emollients (54).

Ingredients and possible risks of emollients

Urea may cause irritation or stinging sensation especially if applied to lesional skin. Some dermatologists are reluctant to use urea under the age of two years. Toddlers should be treated with lower concentrations than adults (3). Glycerol seems better tolerated (less smarting effect) than urea plus sodium chloride (55). Usually, the recommendation is to use emollients immediately after bathing and soft pad drying. A small study suggests that an emollient applied alone without bathing may have a longer duration as measured by capacitance (56).

Propylene glycol is easily irritating in young children aged less than two years and should not be used for toxicity reasons in these young children. There is concern that the large preventive use of emollients containing intact proteins such as peanut allergens (57) or colloidal oat meal (58) may increase the risk of skin sensitization and allergy. Only emollient preparations devoid of proteinaceous allergens and haptens known to cause contact allergy frequently (such as lanolin/wool wax alcohol or methylisothiazolinone) should be used, especially in the most vulnerable age group before the age of two years.

Emollients containing tannin- and ammonium bituminosulphonate (ichthammol) may be a useful addition to the basic treatment regimen, especially in mild disease or if TCS treatment is not possible from a patient's perspective, e.g. corticophobia (steroid phobia) (59).

Sole use of emollients without sufficient topical anti-inflammatory therapy involves a considerable risk for disseminated bacterial and viral infection of AE, which is already increased in AE patients (60).

Emollients "plus"

In the last years, several non-medicated products for topical treatment of AE are available on the market, which contain active ingredients, but are neither fulfilling the definition of nor needing a license as a topical drug. These products may contain for example saponins, flavonoids and riboflavins from protein free oat plantlet extracts, or bacterial lysats from *Aquaphilus dolomiae* or *Vitreoscilla filiformis* (61). These lysats both improve AE lesions and influence the skin microbiome of AE patients (62, 63). In vitro and clinical research data from different laboratories have provided some background information on molecular targets and possible mode of action of these active emollients "plus" (64-66).

Evidence of emollient efficacy

Certain moisturizers could improve skin barrier function in AE and reduce skin susceptibility to irritants. It was clearly demonstrated that long-term emollient therapy improves AE-associated xerosis (67). Simple stand-alone emollient application for one week may improve mild to moderate AE (68). A comparative study showed that an over-the-counter moisturizer could be as clinically effective as more expensive barrier creams in the management of mild to moderate childhood AE (69). Another study in adult AE patients suggested an effect of coconut oil on staphylococcus aureus carriage (70). In addition, the daily use of emollients from birth may significantly reduce the incidence of AE in a high-risk population (71, 72). As the major limitation of these two promising trials is their relatively short duration of half a year, longer trials are currently performed.

Evidence of steroid sparing effects of emollients

1. Short-term (3-6 weeks)

Several studies in children (54, 73) and one in a mixed children-adult population (74) showed a variable but consistent evidence of short-term steroid sparing effect in mild to moderate AE.

2. *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 showed comparable results for intermittent emollient therapy and time to relapse, using comparable study designs in adults and children (75, 76).

Recommendations

Emollients should be prescribed in adequate amounts and these should be used liberally and frequently, in a minimum amount of 250 g per week for adults (3b,C).

Emollient bath oils and soap substitutes should also be used. Emollients with a higher lipid content are preferable in winter time (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 or topical calcineurin inhibitors is required first (2a,B).

Dietary intervention

Food allergens, pre- and probiotics

Food allergy has been well documented in approximately one third of children with moderate-severe AE (77). Among food allergens, cow's milk, hen's egg, peanut, soy, nuts and fish are most frequently responsible for AE exacerbation in young children, with age-dependent variations in causally incriminated food (78). In older children, adolescents and adults pollen associated food allergy should be taken into account (79, 80).

Response patterns to food allergens

Three different clinical reaction patterns in patients with AE have been described, depending on the type of symptoms and their time of onset (78, 81).

Immediate-type, non-eczematous reactions are usually IgE mediated, occur within 2 hours after the administration of the allergen, with skin manifestations such as urticaria, angioedema, flush, and pruritus or other immediate type reactions of the gastrointestinal tract, the respiratory tract, or the cardiovascular system in the sense of anaphylaxis. Cutaneous manifestations occur in 74% of patients. In addition, children might develop a transient morbilliform rash 6 to 10 hours after the initial immediate reaction, disappearing within a few hours and considered as "late-phase" IgE-mediated response (81, 82).

Isolated eczematous delayed-type reactions typically occur 6 to 48 hours after the administration of the allergen with flares of eczema on predilection sites of AE, suggestive for a non-anaphylactic pattern.

A combination of the two above-mentioned patterns with an immediate-type reaction followed by an eczematous delayed-type reaction has been described in approximately 40% of children (83).

Sensitization to food can be identified by means of a detailed clinical history in combination with in vivo tests (skin prick tests, 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 skin prick tests (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 gives 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 test (APTs) are performed with self-made food material using a 1/10 dilution in saline of the fresh food applied for 24-48 hours on non-lesional skin (84). Food APT is not standardized for routine use. So far, APTs have demonstrated to improve the accuracy of skin testing in the diagnosis of allergy to cow's milk, eggs, cereals, and peanuts in patients with AE (85-88). Whereas immediate-type reactions are associated with SPT positivity,

delayed reactions are related to positive responses to APTs. However, double-blind placebo-controlled food challenge (DBPCFC) remains the “gold standard” for the diagnosis of FA (89).

Oral food challenge (OFC) should always be performed under medical supervision with emergency equipment available, particularly after long-lasting elimination of the culprit food. Practically, OFC should be performed according to standardized protocols considering variables associated with food matrix, doses and time intervals (90). In AE the major flaw is that DBPCFC might not offer the opportunity to exclude placebo reactions or coincidental influences of other trigger factors of AE during the prolonged challenge period. Therefore in AE the evaluation of delayed reactions after 24 hours or 48 hours by trained personal is mandatory (83). Challenge tests based on repeated exposure to food enable the assessment of delayed adverse responses (83).

Unfortunately, the effects of dietary interventions on the course of AE have been studied only in a few controlled studies. In a systematic review (11) eight randomised, controlled studies examining the effect of an elimination diet on existing AE were identified and summarized in the following way: a) Elimination diets are difficult to carry out even in a motivating atmosphere during a clinical study. b) The drop-out-rate in AE studies is particularly high in studies on diets. c) 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. d) There is no evidence for a benefit in the use of elementary or few food restricted diets in unselected patients with AE.

A Cochrane systematic review based on nine randomized controlled trials concluded that eliminating egg from the diet in those who had positive specific IgE to eggs proved beneficial (91). The American Academy of Dermatology recommended egg restriction in the subset of patients with AE who were found to be clinically allergic to eggs (92), but this approach should also be followed for other food allergens proven relevant in individual patients.

Although progress has been considerable, there are no simple strategies to prevent the development of AE and food allergy in infants. The recent publication of randomized trials, such as the Learning Early About Peanut Allergy (LEAP) (93) and Enquiring About Tolerance (EAT) (94) studies, have given some support to the notion that early oral ingestion of food may protect from sensitization and allergy later in life. The oral introduction early in the first year of life at a “window of opportunity“ of time between 4 and 6 months of age may actually protect children by facilitating the induction of tolerance (95). Epidemiological studies have shown a significant association between the diversity of foods given in the first year of life and protection form atopic eczema (96).

Pre- and probiotics

Probiotics such as lactobacillus mixtures have been studied in AE, and have been shown to induce improvement (97). Other studies failed to show significant effects (98, 99). In a study with 800 infants the effect of a prebiotic mixture was investigated and found to have beneficial effects in preventing the development of AE (100).

Non-pathogenic bacterial strains like *Vitreoscilla filiformis* or *Aquaphilus dolomiae* have been used as sources for bacterial lysates for topical therapy of AE (see chapter: Topical therapy).

Previous systematic reviews on probiotics for the treatment of AE have consistently concluded a lack of effect in children (101). On the basis of the existing literature, with only one group showing positive results in a controlled study, the guideline group decided not to give a recommendation for treatment with lactobacilli in AE. It may well be that a preventive effect of pre- or probiotic mixtures will be shown in the future; consultation of the S3 guideline on “prevention on allergy” is recommended (21).

Summary of evidence

Food sensitization occurs in about 50 % of children with severe AE. The relevance can be evaluated by oral provocation tests, best performed as double-blind placebo-controlled food challenge. (1a)

Food allergy plays a role for disease exacerbation in 30 % of AE children, most often against basic foods such as hen’s egg or cow’s milk. Pollen-associated food allergy can occur in all ages. (2a)

Food elimination diets represent a major impairment in quality of life and are not easy to perform. (2a)

There is evidence that elimination of basic foods in food allergic children can improve the AE. (1a)

The persistence of food allergy can be evaluated by oral provocation after 1 or 2 years. (3a)

There are no long-term studies to the effect of food elimination diets in AE. (-)

There is conflicting data on prevention or improvement of AE during uptake of pro-biotics such as lactobacillus preparations (1b).

Recommendations

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

Primary prevention of food allergy associated AE is recommended with exclusive breast milk feeding until 4 months of age. (2-3,C)

If breast milk is lacking in low risk children (general population), conventional cow’s milk formula is recommended. (2-3,C)

If breast milk is lacking in high-risk children (one first degree relative with physician diagnosed allergic symptoms), a documented hypoallergenic formula is recommended. (1, B)

Introduction of complementary foods is recommended between 4 and 6 months of age in low and high-risk children irrespective of an atopic heredity. (1-2, B)

A certain diversity of foods selected should be observed during the introduction between 4 and 6 months of age (1, D)

Topical anti-inflammatory therapy

Topical treatment: overall principles

Effective topical therapy depends on three fundamental principles: sufficient strength, sufficient dosage and correct application (3). Many formulations are available especially for corticosteroids, and the choice of formulation has a strong impact on the efficacy of the resulting drug. Topical treatment should always be applied on hydrated skin, especially when using ointments. Patients with acute, oozing and erosive lesions and children sometimes do not tolerate standard topical application, and may first be treated with 'wet wraps' until the oozing stops. Wet wrap medications are highly effective in acute AE and improve tolerance. The use of wet-wrap dressings with diluted corticosteroids for up to 14 days (usual is rather up to 3 days) may be 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 (102-105). However, this treatment approach is not standardized yet, and the evidence that it is more effective than conventional treatment with topical steroids in AE is not of high quality. Simple or occlusive medications in less sensitive skin areas and for brief time periods may also increase efficacy and speed up lesion resolution. Even without wet wraps, topical therapy may be time consuming, and deserves attention. One well-conducted treatment per day is usually sufficient but acute flares 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 now an alternative, which is the proactive treatment concept. Proactive therapy is defined as a combination of predefined, long-term, anti-inflammatory treatment applied usually twice a week to previously affected areas of skin in combination with liberal use of emollients on the entire body and a predefined appointment schedule for clinical examinations (106). The proactive regimen is started after all lesions have successfully been treated by a regular anti-inflammatory therapy (by either steroids or topical calcineurin-inhibitors) in addition to ongoing emollient application on previously unaffected skin. Clinical trial data are available for a number of steroid products as well as for tacrolimus ointment (107), but topical steroids are usually approved only for a very limited period of time such as a few weeks. Studies investigating topical steroids for proactive treatment are usually conducted only for 16 weeks, whereas studies with tacrolimus ointment have shown good results for 52 weeks in both children and adults. The duration of the proactive management is usually adapted to the severity and persistence of the disease (108). The applied amount of anti-inflammatory topicals should also follow the fingertip unit rule (see chapter: Emollient therapy).

Glucocorticosteroids

Topical glucocorticosteroids (TCS) 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. Anti-inflammatory effects in AE were

reported by different investigators (109, 110). With mild disease activity, a small amount of topical corticosteroid 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, roughly adapted to affected body surface area), associated with a liberal use of emollients generally allows a good maintenance. Such monthly amounts of even potent topical steroids usually do not have adverse systemic or local effects. Twice weekly application of fluticasone or methylprednisolone aceponate significantly reduced the risk of relapses of AE in a proactive strategy (109-112).

Several factors should be considered when choosing a topical corticosteroid, including potency, galenic formulation, patient age and body area to which the medication will be applied. The potency of topical corticosteroids is grouped by potency according to Niedner from mild (group I) to super-potent (group IV) (113). Prescribers should know this classification, as they should know that the US-American classification is different and ranges from VII (weakest) to I (strongest). In France, this classification is even different. Super potent TCS (group IV) are not recommended for AE treatment, especially not in children (3). Potent and very potent corticosteroids of group III and IV are more likely to cause depression of adrenal function than group I and II treatments, but their systemic effects will decrease more quickly due to more rapid restitution of the skin barrier (114). Treatment of the face and especially the eyelid region should be restricted to mild TCS (group I and II). Chidren should be treated with less potent TCS than aduts. In addition, there are different generations of substances, which may differ in their risk-benefit ratio.

Itch is the key symptom for evaluation of response to treatment, and tapering should not be initiated before the itch has largely improved. Two applications per day may be necessary to reduce the itch, but one well-conducted, correctly dosed treatment per day may be sufficient (115, 116). Dose tapering is usually applied to avoid withdrawal rebound, although no controlled studies have demonstrated its usefulness. Tapering strategies consist of switching to a less potent corticosteroid, or keeping a more potent one while reducing the frequency of application (intermittent regimen). The most constructive way to spare steroids and avoid steroid-related side-effects is to use them intensively during the acute flares (3). Continuous emollient skin care combined with early anti-inflammatory intervention is also very important to stabilize the disease and prevent flares (117).

Side-effects of topical corticosteroids comprise a variety of skin changes mostly in the sense of skin atrophy – except from contact allergy to glucocorticosteroid substances. The skin changes manifest as thinning of the skin, development of teleangiectasias (rubeosis steroidica), spontaneous scars (“pseudocicatrices stellaires”, ecchymosis, striae distensae (stretch marks). A “dirty neck” (cutis punctata linearis colli) and hypertrichosis may develop. In infants, inappropriate use of TCS in the diaper area can lead to granuloma gluteale infantum or even iatrogenic Cushing’s disease. The risk of ocular complications by topical corticosteroids seems to be low. Development of glaucoma or cataract has been described after systemic glucocorticosteroid application (118).

The use of potent topical corticosteroids in sensitive skin areas (face, neck, folds) should be limited in time to avoid skin atrophy (119). Monitoring by physical examination for cutaneous side effects during long term use of potent topical corticosteroids is very important. The special aspects and potential adverse effects of topical corticosteroids in pregnancy have

been recently revieved (120). The application of topical corticosteroids to the eyelids and periorbital region, even over longer periods of time in adults with AE was not associated to the development of glaucoma or cataracts (118). Application of very potent topical corticosteroids even for brief time periods may result in the drug becoming systemically available and potent enough to induce adrenal gland suppression (121).

In the face a special skin condition called rosacea-like perioral dermatitis is often started by inappropriate, long term use of TCS. The skin seems to become “addicted” to TCS (“red face syndrome” or „corticosteroid addiction syndrome“). This is characterized by rosacea like disease with persistent erythema, burning and stinging sensation. It has been reported mostly on the face and genital area of women primarily in the setting of long-term inappropriate use of potent topical corticosteroids (122).

Patient fear of side effects of corticosteroids (corticophobia) is quite common and should be recognized and adequately addressed to improve adherence and avoid undertreatment (123-125).

The simultaneous combination of topical corticosteroids with topical calcineurin inhibitors at the same site does not seem to be useful. At least in pediatric patients with severe AE, the efficacy and safety profile of pimecrolimus cream 1% combined with fluticasone were similar to that of fluticasone alone (126). Treating sensitive body areas such as the face with topical calcineurin inhibitors while treating other affected body areas with a topical corticosteroid may be a useful and cost effective strategy. Initial treatment with topical corticosteroids may be considered in patients with acute flare to minimize topical calcineurin inhibitor site reactions (108).

Summary of evidence

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

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

Recommendations

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

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

Diluted topical corticosteroids may be used under wet wraps for short-term periods in acute AE to increase their efficacy. (1b, A)

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

Proactive therapy with TCS may be used safely for at least 20 weeks, which is the longest duration of trials (1b, A).

Patient fear of side effects of corticosteroids (corticophobia) should be recognized and adequately addressed to improve adherence and avoid undertreatment. (4C)

Topical calcineurin inhibitors

Two topical calcineurin inhibitors (TCI), tacrolimus ointment and pimecrolimus cream, are licensed for AE treatment. The efficacy of both formulations has been demonstrated against vehicle in clinical trials for short-term (127, 128) and long-term use (129, 130). 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 both adults and children (131, 132). The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a corticosteroid with intermediate potency (133, 134), whereas the latter is clearly more effective than 1.0% pimecrolimus cream (135).

The efficacy of long-term monotherapy with tacrolimus ointment has been shown in children and adults (133, 134, 136). Less data are available for children under 2 years of age (137, 138). Pimecrolimus cream has been studied in infants and children in a combination regimen with topical corticosteroids (139, 140), the latter being given if a flare occurred. Both topical calcineurin inhibitors are approved in the EU from 2 years of age and above. High quality long-term safety data have recently been published on a 4-year tacrolimus and 5-year pimecrolimus studies (141, 142). The cost effectiveness of proactive therapy with tacrolimus has been demonstrated for moderate AE and is even higher in severe AE in a recent study on adult patients (143), whereas the cost effectiveness of first-line treatment with topical calcineurin inhibitors has not been demonstrated 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 flare free intervals, and may be cost-saving in children with moderate or severe AE (144, 145).

In addition, the long-term, effective treatment of patients with AE may have a beneficial effect also on respiratory symptoms and serum IgE (146). 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 decrease skin recall activity, and decrease serum IgE in patients with treatment response.

Safety data of both topical calcineurin inhibitors have been reported in many clinical trials and registries, demonstrating the safety of these drugs in daily routine use. The most frequently observed side effect is a transient warmth, tingling or burning sensation at the application site during the first days of application (127, 135). It starts about 5 min after each application of the drug and may last up to 1 h, but intensity and duration typically disappear within few days (147). Some patients experience a transient worsening of skin conditions. These side effects are more common with tacrolimus ointment than with pimecrolimus cream and when they are applied on acutely inflamed skin. In some patients they are severe enough to induce prompt treatment discontinuation. Initial treatment with topical corticosteroids should thus be considered in patients with acute flare to minimize these site reactions (108).

Generalized viral infections such as eczema herpeticum or eczema molluscatum have been observed during topical calcineurin inhibitor treatment (148, 149), but a high number of clinical trials failed to demonstrate an increased frequency or showed only a transient increase (reviewed in (150-153)). In contrast to corticosteroids, none of the topical

calcineurin inhibitors induces skin atrophy (154, 155). 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. Clinical and preclinical data do not indicate an increased risk of lymphoma (156). In contrast, severe AE as such may carry an independent significant risk for lymphoma (156). The use of topical calcineurin inhibitors is also not associated with increased risk of non-melanoma skin cancer, other malignancies or photocarcinogenicity (142, 157-161). However, given that the long-term use of cyclosporine is associated with an increased photocarcinogenicity risk in solid organ transplant patients, UV protection e.g. with sunscreens has been advised (3). The use of topical calcineurin inhibitors under wet wraps or on erosive lesions may increase systemic absorption.

Clinicians should be aware of the black-box warning on the use of topical calcineurin inhibitors, and may discuss this with patients to improve adherence.

Summary of evidence

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

Tacrolimus 0,1% ointment is more potent than pimecrolimus cream. (1b)

Tacrolimus ointment and to lesser extent pimecrolimus cream may cause burning sensation and transiently worsen AE especially when given on acutely inflamed skin. (1a)

TCI do not cause skin atrophy, glaucoma or cataract. (1a)

Recommendations

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

Instead of treating acute flares with TCI, initial treatment with topical corticosteroids before switching to a TCI should be considered. (-, D).

TCIs are especially indicated in sensitive skin 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)

Upcoming topical therapies

Topical selective phosphodiesterase 4 inhibitors

Crisaborole is a topical phosphodiesterase 4 inhibitor effective in the treatment of AE lesions, which has recently been approved for treatment of mild to moderate AE in patients 2 years of age and older in the United States of America (162, 163). Study data published have focused on treatment of individual skin lesions using global eczema scores, as well as on safety aspects, but do not include SCORAD data or EASI data of the patients treated.

From the published data of the global scores and the individual items of an eczema score, a relatively low efficacy of crisaborole is probable (162). The efficacy of crisaborole is significantly higher than the efficacy of its vehicle. However, the efficacy of crisaborole in comparison to TCI or TCS is difficult to determine. Crisaborole ointment is currently not licensed in Europe.

Other topical phosphodiesterase 4 inhibitors under investigation include OPA-15406 and E6005 (164, 165).

Topical Janus-Kinase (JAK) inhibitors

First promising phase II clinical trial data with the topical JAK- inhibitor tofacitinib have been published (166), but the topical development program was halted. Further similar compounds are in the pipeline for topical as well as for systemic therapy, but none is currently licensed in Europe.

Phototherapy

As most patients affected by AE improve during the sunny summer season, artificial UV radiation is frequently employed in the treatment of AE. On the contrary, a small group of patients will exacerbate following UV radiation.

A recent study has confirmed that 74% of patients affected by mild-moderate AE had complete resolution during summer holidays, 16% had improvement and only 9% had no modification of AE severity, confirming the seasonality of the disease, with improvement during summertime and worsening in the other seasons: Seaside holidays produced a significantly greater improvement than mountains holidays, with complete resolution of the disease in 91% versus 11% of patients ($P<0.01$)(167). While this difference cannot be explained on the sole basis of UV exposure, these data support the hypothesis on the positive effect of UV radiation on AE.

Photobiology of AE treatment

Various pathways and means through which the energy of UV radiation from natural or artificial sources is ultimately transformed into biologic effects within the skin have been suggested, including cutaneous sensory nerves, neuropeptides, neurotrophins, and certain nerve-related receptors (168). In general the effects of UV-light sources on the skin act immunosuppressive, immunomodulating, anti-inflammatory as well as antipruritic, which is obviously an overlapping effect. The known mechanisms of action target immunomodulation through apoptosis of inflammatory cells, inhibition of Langerhans cells and alteration of cytokine production (169). In addition, UV has an antimicrobial effect reducing the colonization of S. aureus, (170) due to its anti-inflammatory effect and improves skin barrier (171). A different explanation could be supported by the role of Vitamin D: a recent study demonstrated that a 2-week course of heliotherapy significantly improved vitamin D balance by increasing serum calcidiol concentration, and caused a marked healing of AE (172). Suppression of Th2 associated cytokines such as IL-5, 13 and 31 have been observed under UVA1 therapy (169). Induction of apoptosis of T-helper cells most probably are related to generation of reactive oxygen species (ROS) (173, 174). Depletion and loss of function of antigen-presenting cells within the epidermis and dermis support immunosuppression via UV light source. Reduction of ICAM1 expression on keratinocytes has been observed and further enhanced via IL-10 induced reduction of γ-IFN (175, 176).

Light sources and current treatment regimen for AE

Heliotherapy uses the exposure to natural sun light under controlled conditions and is part of the therapeutic treatment in so called “climate therapy” at low altitude (Dead Sea) predominantly with UVA (177), at sea level or at high altitude (e.g. Davos) with predominantly UVB (178). The dose in heliotherapy is slowly increased by increasing the time of sun exposure in moderate increments.

The following alternative modalities of UV treatment have been used in AE: UVB (mostly narrowband (NB-UVB) of 311-313 nm and less frequently broadband (BB-UVB), UVA (especially UVA1 of 340-400 nm), combined UVAB, and photochemotherapy where UV can be combined with previous oral or topical administration of photosensitizing drugs such as psoralens - the PUVA photochemotherapy regimen, but the long-term risks of skin cancer noted in psoriasis have drastically limited this modality in Europe. In contrast, classical broad-spectrum UVB phototherapy does not show increased risk for BCC and SCC (179, 180).

Other light therapies have been introduced. Short wave visible light (> 380 nm) (“Blue light”) may have some effects, as indicated in uncontrolled pilot studies (181). There are no controlled studies for this modality. Photopheresis is used in some centers for treatment of selected cases. Positive effects in patients with severe refractory AE have been described. Other devices such as 308 nm monochromatic excimer laser expand the therapeutic options in patients with localized and therapy-resistant AE even though they can treat only limited surfaces (182, 183). Pulsed-dye laser for the treatment of chronic AE is still experimental (184).

Currently the mainstay for phototherapy in Europe is NB-UVB and UVA1. Following concerns relative to PUVA, long-term risks of UV-light therapies have to be considered in particular in children and even more in adults who have received systemic immunosuppressants. Until now, no clinical studies have shown an increase of non-melanoma skin cancer with NB-UVB and UVA1 (185, 186).The benefit/risk ratio of UVA1 medium-high dose (>20-70 J/cm2) is considered as better than that of high or low dose (187-190). Comparison of middle-high UVA1 and NB-UVB does not show significant differences with regard to efficacy and tolerability.

Taking into account the individual tolerability, NB-UVB has been indicated for chronic moderate forms of AE (191) and is currently preferred to BB-UVB because it is less erythemogenic, while high dose UVA1 has been prescribed for more severe phases (192). Furthermore, as highlighted in a recent study, there is a small but significant proportion of psoriasis and AE patients who do not tolerate NB-UVB but demonstrate an excellent clinical response to BB-UVB (193).

Practical aspects of AE treatment

In practice, the choice of a certain UV treatment is limited by the availability of the phototherapy equipment: e.g. UVA1 devices are expensive to buy and to maintain. The biggest drawbacks of UV therapy are that the patient must travel between 3 and 5 times per week and for 6-12 weeks to a site that offers this therapy. In addition, UV light does not effectively treat hairy areas as scalp and skin folds. As a rule, phototherapy is not indicated in the acute stage of AE (except UVA1, which is also effective in managing AE flares), but is more apt to treat chronic, pruritic, lichenified forms and should not be prescribed in those patients who experience a worsening of AE during sun exposure.

At the beginning of phototherapy, a co-medication of topical steroids and emollients should be considered to prevent a possible flare-up. UV therapy has to comply with special

requirements with regard to personnel, documentation, UV protection especially of the eyes, contraindications and technical aspects.

In practice, when prescribed, phototherapy is usually a part of a total treatment plan, i.e. a second-level treatment used especially in adults and much less in children. Phototherapy can improve and even clear AE; it can decrease bacterial colonization and reduce the strength and/or the amount of topical anti-inflammatory drugs needed, but the beneficial effects vary from person to person.

Summary of evidence

Narrow-band UVB has a better safety and efficacy profile compared to broad-band UVB. (1a)

Medium-dose UVA1 is similar in efficacy to narrow-band UVB. (1b)

High-dose UVA1 is more effective in severe phases of AE. (1b)

All UV treatments pose theoretically a long-term risk for development of skin aging and skin cancer, which is best demonstrated for PUVA. (2a)

New devices such as 308 nm excimer laser or visible blue light therapy may expand therapeutic options, but have not been assessed properly in AE. (-)

Recommendations

Medium-dose UVA1 and narrow-band UVB are recommended for treatment of AE in adult patients. (1b, A)

Narrow-band UVB is preferred over broad-band UVB for AE treatment if available. (1a, A)

Co-treatment with topical steroids and emollients should be considered at the beginning of phototherapy to prevent flare-up. (C)

PUVA therapy is not a first choice therapy for safety profile reasons. (1b, A)

New devices such as 308 nm excimer laser are not recommended for treatment of AE patients. (-,D)

Though phototherapy is rarely used in pre-pubertal children, it is not contraindicated; its use depends rather on feasibility and equipment (NB-UVB). (-,D)

Anti-pruritic therapy

Itch is the most important clinical symptom in AE, with particular impact on emotional dimensions of perception as compared to other pruritic dermatoses (194, 195). Concerning pruritus accompanying AE, only few studies investigated the antipruritic effect only. Pruritus was in most studies part of the total symptom score, such as in SCORAD or PO-SCORAD (4, 6). For example, topical and systemic corticosteroids, topical calcineurin inhibitors, cyclosporine and UV-irradiation have significant influence on pruritus while only single studies specifically investigated the relief of pruritus intensity.

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 also be recommended (see: “Basic Therapy” and “Psychosomatic counseling”).

Topical Therapy

Glucocorticosteroids

Topical corticosteroids have anti-inflammatory activity rather than acting as direct anti-pruritic agents (196). However, several studies described the anti-inflammatory effect of topical corticosteroids in AE, in which pruritus was one parameter among others studied. Recent meta-analysis revealed 6 RCT with topical corticosteroids (desonide hydrogel 0.05%, clobetasole propionate lotion, fluticasone propionate 0.05% cream, prednicarbate 0.25% ointment, hydrocortisone 1% and methylprednisolone aceponate 0.1% cream) and showed that those agents significantly reduce itch in AE patients by 34% in comparison to the vehicle usage (197). Topical corticosteroids have a rapid antipruritic effect and can also be used in “proactive” therapy (108).

Calcineurin inhibitors

Topical calcineurin inhibitors relieve significantly pruritus in AE. Itch is completely relieved after the first days of treatment both in adults and children. 22 RCTs were meta-analysed (16 – pimecrolimus 1% cream, 3 – tacrolimus 0.3% ointment, 1 – tacrolimus 0.1% ointment, 1 – tacrolimus 0.03% and 1- tacrolimus 0.01% ointment). Topical calcineurin inhibitors appeared to reduce AE itch significantly by 36% compared to vehicle application (197). Pimecrolimus blocks via TRPV1 the re-accumulation and synthesis of substance P (SP), a major mediator of pruritus in inflammatory skin lesions.

Antihistamines

5% doxepin cream exhibited antipruritic effects in 3 controlled studies in AE; one RCT assessed the efficacy of cromoglycate 4% lotion (197). The meta-analysis of those studies documented that the use of topical antihistamines markedly reduced itch of AE by 27% in patients in comparison to the vehicle. However, topical doxepin therapy is not licensed and not used in any European country due to an increased risk of contact allergy, especially when the treatment exceeds eight days.

Cannabinoid receptor agonist

Topical cannabinoid receptor agonists have been described to exhibit antipruritic and analgesic properties. One cosmetic product containing the cannabinoid agonist N-palmitoylethanolamin was used in a multicenter, large cohort, open label study as adjuvant treatment in AE (74). 2456 patients including over 900 children applied the cream twice daily. Pruritus and the need to use corticosteroids were reduced up to 60%.

Opioid receptor antagonists

One double-blind, vehicle-controlled, randomized cross-over trial was performed with topical μ-opioid receptor antagonist nalmefene. The drug was used during two 7-days periods separated by the wash-out period. The study did not show significant efficacy in reducing the itch intensity in AE (198).

Polidocanol

Case series described the efficacy of a combination of the anaesthetic polidocanol and 5% urea (199). In children with AE, the combination showed a pruritus improvement of 30% in comparison with an emollient (200). Polidocanol is not licensed for AE in Europe, but OTC products are available.

Anesthetics

Local anaesthetics such as benzocaine, lidocaine, 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 AE (201). None of these substances is licensed for AE in Europe, but some OTC products are available.

Capsaicin

Capsaicin, is a naturally occurring alkaloid and the principal pungent of hot chilli peppers. Capsaicin binds to the TRPV1 ion channel, which is present on many itch-mediating C-fibers. Capsaicin has been advocated to be antipruritic in various dermatoses. Concerning AE, experimental studies (202) and case series (203) report on clear itch reduction. No controlled study has been published.

Summary of evidence

There is evidence that topical corticosteroids are effective in the initial phase of AE exacerbation to control pruritus. (1a)

There is evidence that topical calcineurin inhibitors are effective in AE until clearance of eczema to control pruritus. (1a)

There is not enough RCT evidence to demonstrate the efficacy of topical antihistamines, including doxepin in the treatment of AE itch. (1a)

There is no evidence from RCTs that the topical cannabinoid receptor agonist N-palmitoylethanolamin is effective as an adjuvant antipruritic therapy in AE. (4)

There is no evidence that the topical μ-opioid receptor antagonist nalmefene is effective in the management of pruritus in AE. (2b)

There is no evidence that topical anaesthetics and capsaicin is an effective adjuvant antipruritic therapy in AE. (4)

Recommendations

Topical corticosteroids are recommended to control pruritus in the initial phase of AE exacerbation. (1a,A)

Topical calcineurin inhibitors are recommended to control pruritus in AE until clearance of eczema. (1a,A)

Topical polidocanol may be used to reduce pruritus in AE patients. (-,D)

Routine clinical use of topical antihistamines including doxepin, topical cannabinoid receptor agonists, topical μ opioid receptor antagonists or topical anaesthetics, cannot be recommended as an adjuvant antipruritic therapy in AE. (4,C)

There is not enough data available to recommend the use of capsaicin in management of itch in AE patients. (4,B)

UV therapy

UV irradiation relieves pruritus in AE, which has been demonstrated in several studies. A recent systematic review of 19 available RCTs suggests the usage of narrow-band UVB and UVA1 as the most effective in the treatment of AE, including reduction of itch intensity (204). There is no “anti-itch-specific” data for UV therapy available, which would differ from the general recommendations for UV treatment of AE. (See chapter “UV therapy”).

Recommendations

There is evidence that UV-therapy can be used in AE to relief pruritus. Narrow-band UVB and UVA1 seem to be most preferable treatment modalities. (2a,B)

Systemic therapy

Antihistamines

Antihistamines (AH) 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 (205-213). According to a Cochrane search, randomized controlled trials investigating the efficacy of AH monotherapy in eczema patients are lacking (214).

The first generation of sedative AH such as hydroxyzine, clemastine fumarate and dimethindene maleate may allow a better sleep in acute situations with exacerbations of eczema (evidence level D). A significant, but clinically small, antipruritic effect of fexofenadine 60 mg twice daily has been described (215). An effect on itch of a high dosage of 20 to 40 mg cetirizine daily has been observed, but this effect was primarily attributed to sedation (211). In the recent meta-analysis of antipruritics in AE (197) only one RCT study on systemic AH fulfilled the criteria for inclusion and did not show significant improvement of itch in comparison to placebo (211).

In general, AH are safe to use, also for a long period of time (216). There are limited evidence-based data for the antipruritic effect of AH (H1-antagonists) in AE in general, and the effect of both first and second generation AH on pruritus in patients suffering from AE is very limited. AH may decrease urticaria when associated with AD, but this is rarely seen in clinical reality. The ETAC pediatric cetirizine studies showed an effect of AH on food induced urticaria (217). (See also chapter “Other systemic treatment”)

Apremilast

The oral inhibitor of phosphodiesterase 4 (PDE4) apremilast is discussed in part II of the guideline (see chapter “other systemic treatment”).

Leukotriene receptor antagonists

The leukotriene receptor antagonists zafirlukast and zileuton are discussed in part II of the guideline (see chapter “other systemic treatment”).

Opioid receptor antagonists

The μ-opioid receptor antagonist nalmefene was applied in controlled, randomized studies in AE. A dosage of 10 mg and 20 mg each once per day showed significant relief of pruritus in three studies (218-220). In open label trials and one double-blind, placebo-controlled study trial, the only orally active μ-opioid antagonist naltrexone 25 - 150 mg per day showed considerable antipruritic effects (221, 222). Common side effects include anxiety, arthralgia, dizziness, drowsiness, fatigue, vomiting and headache. None of these substances is currently licensed for treatment of AE itch.

Selective serotonin reuptake inhibitors

The antipruritic effect of the selective serotonin reuptake inhibitors paroxetin and fluvoxamin was investigated in an open label trial in dermatological patients. A few patients with pruritus due to AE were included, who responded with considerable reduction of pruritus. In these patients, the pruritus was reduced about half in intensity (maximal antipruritic effect score, 45.0 +/- 7.1%) (223).

Cyclosporine A

See chapter “Systemic Immunosuppression”

Intravenous Immunoglobulin therapy

See chapter “Other systemic treatment”

Mycophenolate mofetil

See chapter “Systemic Immunosuppression”

Nemolizumab

See chapter “Biologics”

Summary of evidence

There is conflicting evidence regarding efficacy of antihistamines (H1-antagonists) for treatment of pruritus in AE, with the majority of studies showing only a weak or no effect on

pruritus. Antihistamines in general, and especially second generation agents, show a good safety profile. (1b)

The opioid receptor antagonists naltrexone and nalmefene may reduce itch in AE patients. Common side effects include anxiety, arthralgia, dizziness, drowsiness, fatigue, vomiting and headache. (1b)

The selective serotonin reuptake inhibitors paroxetine and fluvoxamine may be effective in the treatment of AE-induced itch. Side effects include constipation, diarrhea, dizziness, drowsiness, ejaculatory and erectile dysfunction, decreased libido, insomnia, nausea and headache. (4)

Recommendations

There is not enough evidence to support the general use of both first and second generation H1R-antihistamines for treatment of pruritus in AE. These may be tried for treatment of pruritus in AE patients, if standard treatment with TCS and emollients is not sufficient. (1b, A)

Long term use of sedative antihistamines in childhood may affect sleep quality and is therefore not recommended. (-,D)

The opioid receptor antagonists naltrexone and nalmefene are not recommended for routine treatment of itch in AE patients. (-,D)

The selective serotonin reuptake inhibitors paroxetine and fluvoxamine are not recommended for routine treatment of itch in AE patients. (4,C)

Tables

Table 1 Grades of evidence

1a) Meta-analysis of randomized clinical trials (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
Recommendations (see Table 2) were classified based on the grade of evidence.

Table 2 Classification of strength of recommendation

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

Table 3 Language of recommendations

Wording in standard situations	**Free text explanation**
must be used	This intervention should be done in all patients, unless there is a real good reason not to do it
should be used	Most expert physicians would do it this way, but some would prefer other possible action
may be used	It would be correct to do this intervention, but it would also be correct not to do it; the choice depends largely on the specific situation
is possible	Most expert physicians would do something else, but it would not be wrong to do it
may be used in selected patients only	This intervention is not adequate for most patients, but for some patients there may be a reason to do it
is not recommended	Most expert physicians would not choose this intervention, but some specific situation may justify its use
must not be used	This intervention is inadequate in most situations

Table 4: Topical drugs for treatment of atopic eczema

	TCS class II	TCS class III	Tacrolimus	Pimecrolimus
overall recommendation	+ default treatment	+ short term flare treatment	+ long term maintenance	+ children, facial lesions
most important side effects	skin atrophy teleangiectasia striae distensae	skin atrophy teleangiectasia striae distensae	initial burning/stinging	initial burning/stinging
suitable for long term treatment	sometimes	no	yes	yes
suitable for proactive therapy	yes♦	yes♦	yes*	no
suitable for children > 2 years of age	yes	sometimes, see text	yes*	yes*
suitable for babies < 2 years of age	yes	diluted use	yes♦	yes♦
suitable during pregnancy	yes	yes	possible with strict indication♦	possible with strict indication♦
suitable during lactation	yes	yes	possible with strict indication♦	possible with strict indication♦

♦ off label use * licensed use

Table 5: Upcoming topical drugs for treatment of atopic eczema

	Substance code	Target	Substance class	Development phase	Registration status	Trial data	Adverse drug effect signals	Recommendation
Crisaborole	AN2728	phospho-diesterase 4	PDE4 blocker	IV	app. USA	more effective than vehicle, no comparative study	application site pain	
	OPA-15406	phospho-diesterase 4	PDE4 blocker					
	E6005	phospho-diesterase 4	PDE4 blocker					

♦ see full text
PDE: phosphodiesterase; app: approved;

Treatment recommendation for atopic eczema: adult

- For every phase, *additional* therapeutic options should be considered
- Add antiseptics / antibiotics in cases of superinfection
- Consider compliance and diagnosis, if therapy has insufficient effect
- Refer to guideline text for restrictions, especially for treatment marked with [1]
- Licensed indication are marked with [2], off-label treatment options are marked with [3]

SEVERE: SCORAD >50 / or persistent eczema	Hospitalization; systemic immuno-suppression: cyclosporin A[2], short course of oral glucocorticosteroids[2], dupilumab[1,2], methotrexate[3], azathioprin[3], mycophenolate mofetil[3]; PUVA[1]; alitretinoin[1,3]
MODERATE: SCORAD 25-50 / or recurrent eczema	Proactive therapy with topical tacrolimus[2] or class II or class III topical glucocorticosteroids[3], wet wrap therapy, UV therapy (UVB 311 nm, medium dose UVA1), psychosomatic counseling, climate therapy
MILD: SCORAD <25 / or transient eczema	Reactive therapy with topical glucocortico-steroids class II[2] or depending on local cofactors: topical calcineurin inhibitors[2], antiseptics incl. silver[2], silver coated textiles[1]
BASELINE Basic Therapy	Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests)

Treatment recommendation for atopic eczema: children

- For every phase, *additional* therapeutic options should be considered
- Add antiseptics / antibiotics in cases of superinfection
- Consider compliance and diagnosis, if therapy has insufficient effect
- Refer to guideline text for restrictions, especially for treatment marked with [1]
- Licensed indication are marked with [2], off-label treatment options are marked with [3]

SEVERE: SCORAD >50 / or persistent eczema	Hospitalization, systemic immuno-suppression: cyclosporin A[3], methotrexate[3], azathioprin[3], mycophenolate mofetil[1,3]
MODERATE: SCORAD 25-50 / or recurrent eczema	Proactive therapy with topical tacrolimus[2] or class II or III topical glucocorticosteroids[3], wet wrap therapy, UV therapy (UVB 311 nm)[1], psychosomatic counseling, climate therapy
MILD: SCORAD <25 / or transient eczema	Reactive therapy with topical glucocortico-steroids class II[2] or depending on local cofactors: topical calcineurin inhibitors[2], antiseptics incl. silver, silver coated textiles[1]
BASELINE Basic Therapy	Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests)

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Consensus based European Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis) in Adults and Children Part II

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Declaration of Conflict of Interest

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List of Abbreviations

AAD	American Academy of Dermatology
AD	Atopic dermatitis
AE	Atopic eczema
AEGIS	3-trimethylsilylpropyl-dimethyloctadecyl ammonium chloride
AH	Antihistamines
AGREE	Appraisal of Guidelines Research and Evaluation
APT	Atopy patch test
ASIT	Allergen-specific Immunotherapy
AZA	Azathioprine
BB-UVB	Broadband ultraviolet B
BCC	Basal Cell Carcinoma
BO	Borage oil
CAM	Complementary alternative medicine
CAP-FEIA	CAP Fluorescence Immunoassay
CHM	Chinese herbal medicine
DBPC	Double-blind placebo-controlled
DBPCFC	Double-blind placebo-controlled food challenge
DHA	Docosahexaenoic acid
EADV	European Academy of Dermatology and Venereology
EASI	Eczema Area and Severity Score, a signs score
EAT	Enquiring About Tolerance
EC	Eczema coxsackium
EC-MPS	Enteric-coated mycophenolate sodium
EDF	European Dermatology Forum
EFA	European Federation of Allergy and Airways Diseases Patients' Associations
EH	Eczema herpeticum
EPO	Evening primrose oil
ETFAD	European Task Force on Atopic Dermatitis
EU	European Union
EV	Eczema vaccinatum
FA	Food allergy
FTU	Fingertip unit
GAAPP	Global Allergy and Asthma Patient Platform
HBD	Human-ß-defensin
HDM	House Dust Mite
HTA	Health Technology Assessment
H1R	Histamin 1 receptor
IA	Immunoadsorption
ICAM1	Intercellular Adhesion Molecule 1
IGA	Investigators Global Assessment, a signs score
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukin
IVIG	Intravenous immunoglobulins
IFN-α	Interferon alpha
IFN-γ	Interferon gamma

JAK	Janus kinase
LEAP	Learning Early About Peanut Allergy
LTC4	Leukotriene C4
LTD4	Leukotriene D4
LTE4	Leukotriene E4
MCV	Molluscum contagiosum virus
MMF	Mycophenolat Mofetil
MTX	Methotrexate
mTLSS	modified Total Lesion Symptom Score
NB-UVB	Narrow band Ultraviolet B
OFC	Oral food challenge
OTC	Over the counter
PDE 4	Phosphodiesterase 4
PE	Patient education
PO-SCORAD	Patient-oriented Scoring of Atopic Dermatitis
PUVA	Psoralen and ultraviolet A
RCT	Randomized controlled trial
ROS	Reactive oxygen species
SASSAD	Six Area Six Signs Atopic Dermatitis score
SCC	Squamous Cell Carcinoma
SCIT	Subcutaneous Immunotherapy
SCORAD	Scoring of Atopic Dermatitis, a composite score
SLIT	Sublingual Immunotherapy
SPT	Skin prick test
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TPMT	Thiopurine methyltransferase
TSH	Thyroid-stimulating hormone
Th1	T helper 1 cells
Th2	T helper 2 cells
Th17	T helper 17 cells
UV-light	Ultraviolet light
VOCs	Volatile organic compounds
VZV	Varicella-zoster Virus
QoL	Quality of life
TSLP	Thymic stromal lymphopoietin

Abstract

The existing evidence for treatment of atopic eczema (atopic dermatitis, AE) was evaluated using the national standard Appraisal of Guidelines Research and Evaluation (AGREE). The consensus process consisted of a nominal group process and a Delphi procedure. This second part of the guideline covers antimicrobial therapy, systemic treatment, allergen specific immunotherapy, complementary medicine, psychosomatic counselling and educational interventions, whereas the first part covers methods, patient perspective, general measures and avoidance strategies, basic emollient treatment and bathing, dietary intervention, topical anti-inflammatory therapy, phototherapy and antipruritic therapy.

Management of AE must consider the individual clinical variability of the disease. Systemic immuno-suppressive treatment with cyclosporine, methotrexate, azathioprine and mycophenolic acid are established options for severe refractory cases, and widely available. Biologicals targeting the T helper 2 pathway such as dupilumab may be a safe and effective, disease modifying alternative when available. Oral drugs such as JAK inhibitors and Histamin4 receptor antagonists are in development. Microbial colonization and superinfection may cause disease exacerbation and can require additional antimicrobial treatment. Allergen-specific immunotherapy with aeroallergens may be considered in selected cases. Psychosomatic counselling is recommended especially in stress-induced exacerbations. Therapeutic patient education (“Eczema school”) is recommended for children and adult patients.

General measures, basic emollient treatment, bathing, dietary intervention, topical anti-inflammatory therapy, phototherapy and anti-pruritic therapy have been addressed in the first part of the guideline.

Key words: Atopic eczema, atopic dermatitis, management, therapy, guideline

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Antimicrobial therapy

In patients with AE, the inflammatory micro-milieu initiated by TSLP, IL-4 and IL-13 may downregulate the cutaneous antimicrobial peptides such as cathelicidin LL-37, dermcidin, human β-defensins HBD-1, HBD-2, and HBD-3 (1, 2). This is one of the reasons why these patients are more susceptible to secondary skin infections, which tend to generalize (2). The understanding of colonization and infection in AE has largely increased by structured investigation of the human microbiome in the context of AE. Flares of AE are significantly associated with a *S. aureus*-caused loss of diversity in the cutaneous microbiome, which is not significant if patients have followed a proactive therapy regimen before the flare (3).

Anti-bacterial

In up to 90% of AE patients even the normal looking skin is extensively colonized by *Staphylococcus aureus.* This bacterium is a major trigger of AE, as it leads to inflammation through the release of superantigen toxins, which enhance T cell activation of superantigen specific and allergen-specific T cells, expression of IgE anti-staphylococcal antibodies and as it increases expression of IL-31 which leads to pruritus (4). Scratching favors binding of *S. aureus* to the skin, and the increased amount of *S. aureus* derived ceramidase aggravates the skin barrier defect. Moreover, superantigen production increases expression of alternative glucocorticoid receptors that do not bind to topical corticosteroids, which leads to resistance (5). Biofilm formation by AE-associated staphylococci most certainly also plays a major role in the occlusion of sweat ducts and leads to inflammation and pruritus (6). Recent investigations have shown that besides *S. aureus* the dysbalance of skin microbiome may play an important role in AE pathophysiology (7, 8). New developments in emollients are the incorporation of active compounds that repair the barrier function or influence the microbiome of AE with bacterial lysates from Aquaphilus dolomiae or Vitreoscilla filiformis species (9). A better understanding of the skin microbiome in AE is a promising direction for the development of new treatment strategies.

A systematic review of 26 studies including 1229 participants showed no clear beneficial evidence of antiseptic bath additives or soaps, or of antimicrobial agents added to topical therapies in non-infected atopic dermatitis. Nevertheless, if there is no response to topical glucocorticosteroids or calcineurin inhibitors, or evident infection, the use of topical antiseptics can be considered, and these are preferred over topical antibiotics with regard to the development of bacterial resistance (10). Sodium hypochlorite 0.005% is not only antiseptic but enhances epidermal thickness and proliferation (11). Its intermittent use showed a significant decrease of AE severity (12). Systemic antibiotics should only be used in case of apparent and extensive bacterial superinfection. On the basis of current resistance spectra, cephalexin, or another first-generation cephalosporin can be recommended. Children with AE seem to have a much lower rate of community-acquired methicillin resistant *S. aureus* infection compared to the general pediatric population (13). In any case treatment with emollient and corticosteroids or topical calcineurin inhibitors should be continued.

Underestimated sources of bacteria are cream and ointment containers, of which up to 53% are contaminated, up to 25% with *S. aureus.* Thus the following recommendations seem to be useful (14): 1.) Keep open moisturizers in refrigerator; 2.) Use pumps or pour bottles rather than jars; 3.) Avoid direct contact with hands and decant; 4.) Avoid sharing personal hygiene items.

Antimicrobial textiles

Silver-impregnated textiles have shown significant antimicrobial activity, as well as improvement of localized SCORAD in an unblinded, side-to-side controlled clinical trial (15). In patients with uninfected AE, the use of silver impregnated textile compared to cotton underwear did not reduce AE severity (16-18). However, some functional textiles (silver-coated, acid-coated and silk textiles) as well as Chitosan, a natural biopolymer with immunomodulatory and antimicrobial properties, may possibly improve AE manifestations, as they decrease skin colonization by *S. aureus,* and they reduce itch (19). Some of these newer options are still under investigation and there seem to be some concern about the safety of silver-coated textiles in infants and toddlers. AEGIS-coated silk textiles did not show clinical benefit in a well-controlled, multicenter clinical trial (20).

Anti-viral

Viral infections including herpes simplex, varicella zoster, molluscum contagiosum, smallpox and coxsackie viruses occur more frequently in AE patients than in healthy individuals, with a tendency to disseminated, widespread disease (21).

Eczema herpeticum (EH), a disseminated herpes simplex virus infection, is a potentially serious complication of AE that requires immediate medical action. Patients, mostly children, present with disseminated vesicles, fever and lymphadenopathy and can develop complications such as keratoconjunctivitis, meningitis and encephalitis. Predisposing factors of EH are early onset of AE, severe or untreated forms of AE, filaggrin deficiency and high total serum-IgE level (21). Pre-treatment with topical corticosteroids does not seem to imply an increased risk of developing EH whereas topical calcineurin inhibitor may do so and should be discontinued immediately (22). Mainstay of EH therapy is a systemic treatment with aciclovir or valaciclovir, in a majority of cases administrated intravenously (23). Treatment should be started immediately once the clinical diagnosis is made (24).

Varicella-zoster virus (VZV) infection in an immunocompetent child is usually a mild, self-limited disease. This infection is, however, known to facilitate secondary local or systemic bacterial infection, which is cause for particular concern in AE children. Earlier studies demonstrated the safety and efficacy of VZV vaccination in these children who appear to benefit from this vaccination (25). Moreover, in children with AE, common childhood immunization in the first year is not associated with an increased risk of more severe AE or allergic sensitization; also immune response to VZV vaccine is comparable to healthy children (26). Therefore parents of atopic children should be encouraged to fully immunize their children.

Molluscum contagiosum virus (MCV) infection is in general benign and self-limited, but in patients with AE dissemination is frequent and therefore treatment is recommended. A large

variety of topical treatments have been reported such as cantharidin, potassium hydroxide, tretinoin cream, topical cidofovir, and others (27). Physical therapies including cryotherapy and curettage are also effective, but not always well tolerated in pediatric patients (28). Topical treatment of AE with TCS may be continued during MCV infection.

Eczema vaccinatum (EV) is a complication of smallpox vaccination known to occur in AE patients. The vaccinia virus disseminates and causes an extensive rash and severe systemic illness with a mortality rate estimate at 5-40% (29). Therefore smallpox vaccination is contraindicated in patients with a history of or currently active AE (30). The existence of an attenuated vaccine and three antiviral drugs, in addition to vaccinia immunoglobulin, provides means of preventing or treating EV (31, 32). Should a smallpox outbreak necessitate an emergency mass vaccination, the choice of vaccination strategies, such as ring or mass vaccination, has to be determined by policymakers.

Eczema coxsackium (EC) is a disseminated form of coxsackie virus infection mostly occurring in children with active AE lesions. The coxsackie virus A6 strain leads to atypical disease manifestations, which are classified as diffuse form (lesions extended to the trunk), acral form (lesions with a mainly acral distribution), or eczema coxsackium (disseminated lesions on preexisting eczematous areas) (33). Symptomatic treatment includes use of topical steroids and wet wrap therapy (34, 35).

Regional vaccination programs should be followed by all AE patients as recommended. The denial of vaccination because of diagnosed AE is a misconception possibly leading to fatal consequences (see chapter: general measures).

Anti-fungal

Despite its role as a commensal on healthy human skin, Malassezia spp. is attributed a pathogenic role in AE, as it may interact with the local skin immune response and barrier function. The precise mechanisms by which Malassezia spp. may contribute to the pathogenesis of AE are not fully understood and remain to be elucidated (36). Several randomized, placebo controlled trials investigated the benefit of topical or systemic antifungal treatment for AE patients (37, 38). The ambiguous results of these clinical trials might be attributed to a selection bias. It can be speculated that antifungal therapies are more effective in certain subgroup of AE. It seems for example that antifungal therapy shows beneficial effects in patients with a head-neck-type distributed AE and detectable IgE-mediated sensitization against Malassezia (39). It has also been shown that sensitization against this skin-colonizing yeast can correlate with disease activity (40). The most common class of antifungal drugs prescribed for AE patients are azoles such as ketoconazole and itraconazole which have also some anti-inflammatory properties (38). Due to a better benefit side effect ratio imidazole derivates (fluconazole or itraconazole) should be prescribed instead of ketoconazole for systemic treatment. In summary, antifungal treatment with either topical ketoconazole or ciclopiroxolamine or systemic itraconazole or fluconazole can be considered for those patients who suffer from head–neck dermatitis, particularly for those who are characterized by clear IgE-sensitization to Malassezia spp.

Summary of evidence

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

A Cochrane review showed no clear beneficial evidence to antiseptic substances in non-infected AE. (4)

Topical glucocorticosteroids and calcineurin inhibitors reduce the colonization rate of S. aureus in AE. (4)

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

AEGIS-coated silk garments do not show clinical benefit over standard care (2b).

VZV vaccination is safe, efficacious and beneficial for children with atopic dermatitis. (2a)

An antifungal therapy may be efficient in some AE patients, mainly in those suffering from the „head and neck“-variant of AE or with demonstrated IgE-sensitization to *Malassezia spp*. (2b)

Recommendations

A short course of systemic antibiotics, such as cephalosporin, may be considered in AE patients clinically infected with S. aureus. (2b, B)

The long-term application of topical antibiotics is not recommend due to the risk of increasing resistances and sensitizations. (2, D)

Treatment with topical antiseptic drugs – including antiseptic baths e.g. with diluted sodium hypochlorite - should be considered, if clinical signs of bacterial superinfection are present. (4,C)

Treatment with topical antiseptic drugs – including sodium hypochlorite 0.005% baths – may be considered in patients with treatment resistant, chronic course of AE. (2b,B)

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

VZV vaccination is recommended for children with atopic dermatitis. Parents of atopic children should be encouraged to fully immunize their children. (2a,B)

Topical or systemic antifungal therapy may be effective in some AE patients, mainly in those suffering from the „head and neck“ variant of AE or with demonstrated IgE-sensitization to *Malassezia spp*. (2b,B)

Systemic anti-inflammatory treatment

Immunosuppressive treatment

Oral glucocorticosteroids

Oral glucocorticosteroids are used in many European countries for treatment of AE. Well known side effects limit their use especially for long-term treatment. Funding of expensive clinical trials in the near future is unlikely.

Controlled clinical trial data demonstrating efficacy: There is one controlled trial available that demonstrates lower efficacy of therapy with systemic prednisolone compared to ciclosporine in severe adult AE patients (41). Broad experience from clinical use by many experts indicates some efficacy, as well as prompt rebound after withdrawal.

Summary of evidence

Short term treatment with oral glucocorticosteroids is moderately effective. (1b)

Systemic steroids have a largely unfavourable risk/benefit ratio for treatment of AE. (1b)

Recommendations

Short-term (up to 1 week) treatment with oral glucocorticosteroids may be an option to treat an acute flare in exceptional cases of AE. Restrictive use, largely limited to adult patients with severe AE, is recommended. (-, D)

The daily dose should be adjusted to and not exceed 0,5 mg/kg body weight. (-, D)

Long-term use of oral glucocorticosteroids in AE patients is not recommended. The indication for oral steroids in children should be handled even more cautiously than in adults. (-, D)

Cyclosporine A

Cyclosporine is licensed in many European countries for treatment of AE and is therefore considered to be the first line option for patients with severe disease who require systemic immunosuppressive treatment.

Controlled clinical trial data demonstrating efficacy

Cyclosporine vs. Placebo: A meta-analysis and review of pooled data from 15 RCTs (42) clearly demonstrated the efficacy of cyclosporine in AE with a 55% improvement on average after 6-8 weeks of treatment. Body surface area, erythema, sleep loss and glucocorticosteroid use were reduced in the cyclosporine group. Cyclosporine is more effective than placebo, but there is often prompt relapse if cyclosporine is stopped. All scores are back to pre-treatment values eight weeks after the end of cyclosporine therapy in most patients.

Cyclosporine dose finding study for AE treatment in adult patients: A fixed dosage cyclosporine regimen was evaluated in 106 adults with severe AE (43). Initial treatment was performed with 300 mg/d or 150 mg/d and reduced after two weeks to 50% of the initial daily dose until a final evaluation was performed after eight weeks. Clinical efficacy was detectable after two weeks in both treatment groups, but the higher dose was significantly more effective ($p<0.05$). The authors recommended to start therapy with 150 mg/d, because this regimen showed a lower incidence of serum creatinine increase. It is recommended today to start with a higher dose of 4-5 mg/kg/day to obtain a good initial result unless the patient is old or suffers from relevant concomitant diseases (44). Some patients may tolerate low dose cyclosporine therapy for a longer time than the usually recommended therapy length of 2 years (45).

Continuous or intermittent cyclosporine therapy study of AE in children: Forty children aged 2-16 years were randomized to either a continuous long term or an intermittent short term cyclosporine regimen (46). Both groups showed significantly better results in clinical scores and quality of life assessments. Enhanced sustained improvement was seen in the continuously treated group. As the intermittent therapy was sufficient in some patients but associated with a lower cumulative cyclosporine dose, the authors recommended choosing the regimen on an individual basis.

Cyclosporine or UV Therapy for AE: Cyclosporine was tested against a combined UV/UVB regimen in a one year, open label, multicentre trial involving 72 patients (47). Cyclosporine therapy induced a significantly higher number of days in remission, as compared to UV therapy.

Compounding of Cyclosporine: Micro emulsions of cyclosporine show an earlier onset and higher peak value of efficacy compared to traditional formulations (48). The clinical efficacy evaluated after eight weeks of therapy was, however, identical for both formulations.

Drug safety profile of Cyclosporine: Patients receiving cyclosporine should be monitored for blood pressure and renal parameters, as cyclosporine is known to induce structural and organic kidney damage. Nephrotoxic effects are more likely to occur if the daily dose exceeds 5 mg/kg body weight, serum creatinine values are elevated or elderly patients are treated. Life vaccination is contraindicated during cyclosporine therapy.

Summary of evidence

Many RCTs indicate the efficacy of cyclosporine versus placebo in AE. (1a)

Cyclosporine is also effective in children and adolescent AE patients. (2b)

Self-willed reduction of the recommended cyclosporine dose may reduce the clinical efficacy of cyclosporine and is not recommended. (2b)

A micro emulsion of cyclosporine has the advantage of an earlier onset and peak level of clinical efficacy, which may be useful in short-term treatment. (1b)

Long-term intermittent cyclosporine therapy for one year is more effective than an intermittent UVA/UVB therapy following a 2-3 times weekly regimen. (1b)

Recommendations

Cyclosporine may be used in chronic, severe cases of AE in adults. Treatment should not exceed a two-year continuous regimen. Careful monitoring for potential severe side effects must be performed. (1a, A)

Cyclosporine may be used (off label) in children and adolescent patients showing a refractory or severe course of disease. A detailed patient monitoring, especially of the renal status, is advisable. (2b, B)

The duration of cyclosporin therapy is guided by clinical efficacy and tolerance of the drug. Both short-term and long-term therapy may be useful in AE. (-, D)

Common side effects of cyclosporine (e.g. nephrotoxicity, hypertension) argue against a long-term treatment of AE with cyclosporine. Therefore, an interval of 3-6 months is usally recommended. (-,D)

Cessation of therapy or switch to another systemic drug should be attempted after two years of therapy, although many patients tolerate much longer therapy with low dose cyclosporine. (-,D).

An initial daily dose of 5 mg/kg/d, divided upon two single doses, is recommended. A dose reduction of 0.5-1.0 mg/kg/d every two weeks is recommended, once clinical efficacy is reached. (-,D)

Dose reduction should be considered according to clinical efficacy. Long term treatment prescribing the lowest clinically useful dose may be advisable in selected cases. (-,D)

Since an intermittent dosage regimen (e.g. “weekend therapy”) will lead to lower cumulative doses of cyclosporine and is effective in some AE patients, an individualized dosage regimen is recommended for underage patients. (-,D)

Cyclosporine trough levels do not need to be assessed routinely during therapy. (-,D)

Though there are no controlled studies available regarding the efficacy of vaccination during cyclosporine therapy, there is no evidence for a failure during cyclosporine either. Hence, a cessation of therapy of 2 weeks before and 4-6 weeks after vaccination may be advisable. Clinically, there is no evidence for this recommendation. (-,D)

A combination therapy of cyclosporine with UV-therapy is not recommended, effective UV protection should be used. (-,D)

Azathioprine (AZA)

Azathioprine is used (off label) for many years for treatment of AE in adult patients. Funding of expensive clinical trials in the near future is unlikely.

Controlled clinical trial data demonstrating efficacy: Efficacy of AZA was tested in a randomized, controlled, 6 month, crossover clinical trial involving 37 patients aged 17 to 73 years (49). The drop-out rate was high (12 patients on AZA, 4 patients on placebo). AZA (2.5 mg/kg/d) or placebo was given for three months each in a crossover design. The SASSAD skin severity score was reduced by 26% in the AZA group and 3% in the placebo

group (p<0.01). Pruritus, sleep loss and fatigue improved significantly during AZA, but not during placebo treatment.

Another randomized double blind, placebo controlled, 12 weeks, clinical trial involved 63 outpatients with AE (50). Following a low dose introduction phase, azathioprine was dosed in 42 patients according to the results of a thiopurine methyltransferase (TPMT) polymorphism, which may be indicative for the myelotoxicity of azathioprine – the other 21 patients received placebo. Patients with a normal TPMT activity were treated with 2.5 mg/kg/d AZA, whereas patients with a reduced TPMT activity (heterozygous phenotype) received 1.0 mg/kg/d AZA. The AZA regimen was more effective in AE, as the disease activity dropped by 37% in the azathioprine group and by 20% in the placebo group. None of the patients showed myelotoxic symptoms.

A prospective, randomized controlled trial showed equal clinically relevant improvement of AZA 1.5-2.5 mg/kg/day compared to methotrexate 10-22.5 mg/week after 12 weeks of treatment in adults with severe AE. Both treatments were safe in the short term (51).

Twelve children with severe, recalcitrant AE were treated with oral AZA and followed prospectively. AZA therapy was associated with clinical improvement in all but 1 patient. There were few adverse effects (52).

A retrospective, uncontrolled study investigated 48 children and adolescents aged 6 to 16 years diagnosed with severe AE (53). After three months of therapy, 28 patients showed very good and 13 patients showed good improvement of their symptoms, while 7 patients showed little or no improvement. None of the patients showed myelotoxic symptoms, TPMT activity was determined in all patients before treatment. All patients were started on 2mg/kg/d AZA and the dose was increased to 3mg/kg/d in 14 patients due to insufficient clinical response. The mean time to achieve clinical response was 4 weeks.

A retrospective, uncontrolled study in a heterogeneous group of 17 children and adults with a mean age of 16 years showed significant improvement of SCORAD after 3 and 6 months of AZA, and significant reduction of total serum IgE levels (54).

Safety profile of azathioprine The authors of the Berth-Jones study concluded, that AZA would be an effective and clinically useful drug for treatment of severe AE, but would be associated with a high rate of unwanted drug effects (49). Leukocyte counts and liver enzymes must be controlled during therapy. The higher dose caused gastrointestinal symptoms in 14 patients; leukopenia in 2 and elevated liver enzymes in 8 patients. Long-term efficacy and safety data in AE patients are sparse, but AZA increased the risk of non-melanoma skin cancer and lymphoma in inflammatory bowel disease patients (55).

Summary of evidence

AZA is effective for treatment of severe AE in adults. (1b)

One small prospective clinical trial in children showed efficacy of AZA. (4)

Recommendations

AZA may be used (off label) in adult AE patients, if cyclosporine is either not effective or contraindicated. (1b,A)

AZA may also be used (off label) in children. (4, C)

Patients should be screened for TPMT activity before starting AZA therapy to reduce the risk for bone marrow toxicity by dose adaptation. The suggested dose range is 1-3mg/kg bw/d. (1b,A)

Alternatively, an initial AZA dose of 50mg/day in adults and a slow increase of the dose under close monitoring of full blood and liver function count is possible. (-, D)

In pregnant women, AZA should only be used on strict indication. (-, D)

AZA should not be combined with UV therapy, effective UV protection should be used. (-, D)

Mycophenolate Mofetil (MMF)

MMF is an immunosuppressant drug licensed in many European countries for the treatment of systemic lupus erythematosus and prevention of transplant rejection.

Controlled clinical trial data demonstrating efficacy: There is one controlled trial with enteric-coated mycophenolate sodium (EC-MPS) vs. Cyclosporine A as long-term treatment showing almost equal efficacy (56). Some case reports or uncontrolled clinical trial data from adults indicate that it would be clinically effective in AE (57, 58). There is one uncontrolled retrospective report involving 14 children indicating efficacy in this age group, with MMF 40-50 mg/kg/d in younger children and 30-40 mg/kg/d in adolescents (59) and another including 12 children (60). A fixed dose of 2g MMF per day for adults is common practice in Europe (24).

Drug safety profile of MMF: Gastrointestinal adverse events such as nausea or diarrhoea are the most relevant side effect of MMF. They are most common during initiation of treatment and tend to disappear during long-term treatment. Leukopenia or thrombocytopenia may also occur. Recent data indicate that MMF should be discontinued 6 weeks before a planned pregnancy (61).

Summary of evidence

Positive case reports and uncontrolled clinical trial data indicate that MMF may be effective in AE. (4)

There is no randomized clinical trial data for use of MMF in children or adolescents. (-)

MMF and EC-MPS are both teratogenic substances. (3a)

Recommendations

MMF may be used (off label) for treatment of AE in adults in a dose up to 3 g/d, if cyclosporine is not effective or not indicated. (4,C)

MMF may be used for treatment of AE in children or adolescents. (4, C)

As MMF and EC-MPS are both teratogenic, men and women of childbearing potential must use effective contraception during therapy. (3a, B)

Methotrexate (MTX)

The immunosuppressant MTX is frequently used in psoriasis, but there is little published data on its use in AE. Some clinicians have used this drug in AE with good responses since many years. MTX can be given by oral, intravenous or subcutaneous application. Funding of expensive clinical trials in the near future is unlikely.

Controlled clinical trial data demonstrating efficacy: A randomized trial with MTX vs. Azathioprine showed comparable effects in severe AE (51).

Forty children with severe AE were randomly assigned to receive either methotrexate 7.5 mg weekly or cyclosporin 2.5 mg kg daily for 12 weeks. At week 12, patients in the methotrexate group had a mean reduction in SCORAD which was not statistically different from the cyclosporin treated group. Both drugs were associated with minor adverse effects, none of which required changing the treatment regimen (62).

An open 24 week dose escalation clinical trial involving 12 adult patients investigated the efficacy of increasing doses MTX (63). The starting dose of 10 mg/week was increased weekly in steps of 2.5 mg/week until clinical efficacy was seen. The skin score SASSAD improved by 52% after 24 weeks. The median dose administered was 15 mg MTX/week. Improvement remained stable in 9 patients 12 weeks after end of treatment.

An uncontrolled, retrospective report involving 20 adult AE patients treated with 10 mg/week to 25 mg/week MTX showed response in 16 patients after 8-12 weeks (64). First improvement was observed after a period ranging from 2 weeks to 3 months (mean 9.95 w +/- 3.17). Treatment was more effective in adult onset AE than in childhood onset.

Forty Children with severe AE were randomly assigned to receive either methotrexate 7.5 mg weekly or cyclosporin 2.5 mg/kg daily for 12 weeks. At week 12, patients in the methotrexate group had a mean reduction in SCORAD which was not statically different from the cyclosporin treated group. Both drugs were associated with minor adverse effects, none of which required changing the treatment regimen (62).

Safety profile of MTX:

All available drug safety data for MTX is largely derived from clinical experience from other low dose indications for MTX, indicating liver toxicity and teratogenicity as main areas of concern. There is no AE specific safety data available for MTX.

Summary of evidence

An open, uncontrolled clinical trial, as well as broad clinical experience, indicate that MTX may be effective in AE. (4)

MTX is a teratogenic substance. (3a)

Recommendations

MTX may be used (off label) for treatment of AE in both adults and children. (4,C)

The recommended dosing regimen is similar or slightly lower compared to psoriasis. (D,-)

As MTX is teratogenic, men and women of child bearing potential must use effective contraception during therapy. (3a,B)

Biological agents

Biological agents (Biologics) have been used in dermatology for more than 10 years for other inflammatory skin diseases, especially psoriasis, but so far no registered biologics for AE are available in Europe. Biologics present a relatively new group of therapeutics created by using biological processes that include recombinant therapeutic proteins such as antibodies or fusion proteins. Biologics specifically target inflammatory cells and/or mediators respectively. In AE, biologics may be helpful in reducing inflammation by modulating the number, activation and function of immune cells or the action of cytokines or disease relevant antibodies. Several case reports, pilot studies and retrospective analyses on the effect of biologics in patients with moderate to severe AE refractory to topical and/or systemic therapy have been published, and randomized, placebo-controlled studies evaluating the efficacy and safety of a few biologics in AE are now available.

Approved biologic therapy

Dupilumab

Dupilumab, a fully human monoclonal antibody that blocks the common α-chain of the receptor for interleukin-4 and interleukin-13, has been approved as first line treatment for moderate-to-severe adult AE in the USA in March 2017 and in Europe in September 2017. Dupilumab has previously shown efficacy in patients with asthma and elevated eosinophil levels and now also in AE (65). Randomized, double-blind, placebo-controlled trials involving adults who had moderate-to-severe AE were performed. In 4-week monotherapy studies, dupilumab resulted in rapid and dose-dependent significant improvements in pathophysiological and clinical parametres. Side-effect profiles were not dose-limiting and mostly mild side effects were observed. In a 12 week double-blind study where topical corticosteroids were combined with dupilumab or placebo, the group treated with dupilumab had significantly better effect on both AE activity and pruritus (65). The positive outcome for dupilumab treated moderate to severe adult AE patients was confirmed in a double blind, placebo controlled study involving 380 randomly assigned to different dosages of dupilumab or placebo (66). Recently, the two identical phase III SOLO studies in adults have completed the clinical development program for dupilumab, again confirming the efficacy of dupilumab monotherapy on skin signs and symptoms, and overall improvement of the QoL in AE. A significant proportion of patients achieved an IGA score of clear and almost clear and at least a 75% improvement in EASI score (67). The LIBERTY AD CHRONOS studies indicate maintenance of efficacy over 1 year of continued treatment with dupilumab (68). The safety profile of dupilumab was good, with conjunctivitis being the only adverse event that was observed more frequently with dupilumab than with placebo. In view of all trials published so far, about 1/3 of all treated patients are clear or almost clear in IGA from their AE. Up to 70% of patients achieve an EASI 75 or higher skin improvement, and it takes about 4 weeks to reach the fullclinical outcome. Skin signs, QoL, and symptoms including pruritus significantly improved as early as 2 weeks after treatment initiation. Several ongoing studies involving both children and adolescents will show if these subgroups of the AE population may experience equally positive effects, expanding the treatment indication for dupilumab even further.

Summary of evidence

A number of large, randomized, placebo controlled clinical trials indicate that dupilumab is effective in AE, with the response maintained for at least 1 year of continuous treatment in the majority of patients. (1b)

Dupilumab-treated AE patients did not show systemic side effects in clinical studies, but showed a higher incidence of conjunctivitis. (1b)

Recommendations

Dupilumab is recommended as a disease modifying drug for patients with moderate to severe AE, in whom topical treatment is not sufficient and other systemic treatment is not advisable. (1,a)

Dupilumab should be combined with daily emollients and may be combined with topical anti-inflammatory drugs as needed. (2,b)

Upcoming biologic therapy

Nemolizumab

Nemolizumab, a humanized monoclonal antibody directed against the IL-31 receptor A, has shown efficacy in patients with moderate to severe AE (69). There was a significant improvement in the primary endpoint pruritus, as well as in the objective signs of the AE with, however, less efficacy. Nemolizumab is currently not approved for any indication.

Summary of evidence

A randomized, placebo controlled clinical trial indicates that nemolizumab is effective in treating pruritus in AE patients. (1b)

Nemolizumab-treated AE patients did not show systemic side effects in clinical studies, but showed a higher incidence of peripheral edema. (1b)

Off label use of other traditional Biologicals

Rituximab

The depletion of B cells by an anti-CD20 antibody, rituximab (2x 1000 mg), resulted in a rapid reduction of skin inflammation in all patients with a sustained effect over 5 months in five of six patients. These results may suggest a pathogenic role of B cells in AE, although CD20 may also play a role in some DC-T cell mediated reactions (70). A report on two cases of severe AE receiving rituximab could not confirm these findings (71).

Mepolizumab

Inflammation in AE is characterized by a T helper 2 cytokine expression including interleukin (IL) –5 and eosinophil infiltration. Upon short-term therapy with the anti-IL-5 antibody mepolizumab (2 x 750 mg), a moderate improvement of clinical symptoms was observed, although a rapid depletion of eosinophils in the peripheral blood was noted (72). The patients were not stratified for eosinophilia in this study. Mepolizumab had no effect on atopy patch

test reactions (73). Based on the promising results in AE and the experiences in bronchial asthma therapy, long-term trials with anti-IL-5 antibodies are now performed.

Omalizumab

Most AE patients have elevated serum IgE levels, but the pathogenic role of IgE in AE remains unknown. In a placebo-controlled study in 20 patients, omalizumab administered for 16 weeks failed to improve AE symptoms and itch despite a depletion of free serum IgE and reduction of IgE receptor saturation (74). Other studies reported that accompanying AE significantly improved in patients receiving omalizumab because of severe bronchial asthma (75-77). First explorative open label trials did not indicate good efficacy (78). An open label study on 20 adult patients with severe AE have indicated an increased efficacy of omalizumab in patients with wild type filaggrin status and high levels of phosphatidylcholines (79). An open label study involving 7 treatment refractory, pediatric AE patients treated with omalizumab for 12 to 68 months showed significant improvement of their AE (80). By contrast, a recent small, randomised, trial including 8 children with severe treatment refractory AE treated for 24 weeks with omalizumab or placebo showed no significant clinical differences between the two groups (81) and this was confirmed in another similar study (82). In summary, the data concerning omalizumab are conflicting, and omalizumab cannot be recommended for treatment of AE.

Ustekinumab

By blocking IL-12 and IL-23, ustekinumab can regulate Th1, Th17 and also Th22 pathways, which are reportedly active in AE. Results regarding the use of ustekinumab in severe AE have, however, been conflicting and only case reports have been published so far. Some have reported significant improvement of AE (83) and some have not (84). The first two randomised controlled trials comprising 79 and 33 patients in total have been completed, and results are quite uniform showing no significant decrease in severity scores (85, 86).

Other substances

Some older biologics such as infliximab or efalizumab, which are outdated for use in atopic dermatitis or withdrawn from the market, are not discussed anymore in this version of the guideline.

On the other hand, a number of highly interesting substances are in progress and may soon be registered for treatment of AE. Therefore, the committee decided to produce a table in the addendum on potential new biologics or small molecules for AE “in the pipeline”, which will be continuously updated by the guideline committee. Substances to be included in this table will be, among others, the anti-IL 13 antibody tralokinumab, the anti-TSLP antibody tezepelumab, and the Janus kinase (JAK) inhibitor upadacitinib.

Summary of evidence

None of the traditional biologics has been approved for the therapy of AE in Europe. At present, the use of traditional biologics in AE should be tried only in patients with severe AE refractory to other topical and/or systemic treatment. Beside the lack of efficacy and safety data in AE, the potential side effects must be taken into account before using biologics. On

the other hand, treatment with biologics may provide important information on pathogenetic mechanisms in AE. Today, the imminent availability of Th2-blocking biologics has further reduced the clinical need for experimental therapy with traditional biologics. (-)

Recommendations

A therapy of AE with traditional biologics (rituximab, omalizumab or ustekinumab) cannot be recommended. (4, C)

A therapy of AE with mepolizumab may be tried in selected cases unresponsive to standard therapy. (-, D)

Other systemic treatment

Alitretinoin

Alitretinoin is a retinoid binding both retinoid and rexinoid receptors, thus delivering anti-inflammatory and anti-proliferative effects. It is licensed in some European countries for the treatment of chronic hand eczema irrespectively of its pathogenesis.

Controlled clinical trial data demonstrating efficacy

There is one large, multicenter randomized, placebo controlled clinical trial involving 1032 patients with chronic hand eczema, about one third of which are probably atopic hand eczema patients (87). Improvement of eczema symptoms was seen in 75% of the patients. The response rate of hyperkeratotic hand eczema (49%) and pulpitis sicca type patients (44%) was higher than the dyshidrosiform subtype of hand eczema (33%). The patient group suffering from atopic hand eczema has not been analyzed separately, and extrapalmar symptoms have not been assessed in this trial.

Six patients with AE and prominent hand involvement have been treated with alitretinoin for twelve weeks in an uncontrolled, open label trial (88). Palmar and extrapalmar lesions improved during the trial, as shown by the mTLSS hand eczema score and the SCORAD.

Drug safety profile of alitretinoin

As alitretinoin is highly teratogenic, all females of childbearing potential must adhere to a strict birth control program. Headache is the most frequent clinical side effect of alitretinoin especially in the first two weeks of treatment. Serum lipid and TSH elevation may also occur.

Summary of evidence

Direct evidence from an uncontrolled clinical trial, as well as indirect evidence from a large, double blinded, placebo controlled clinical trial indicates that alitretinoin may be effective in atopic hand eczema. (4)

Alitretinoin is a teratogenic substance. (-)

There is no trial data for its use in children or adolescents. (-)

Recommendations

Alitretinoin may be used for atopic hand eczema in adult patients of non-child-bearing potential unresponsive to topical steroid therapy. (1b,A)

Alitretinoin might lead to an improvement of both extrapalmar and hand lesions in AE patients. (4,C)

Apremilast

Apremilast is a small molecule phosphodiesterase (PDE) 4 inhibitor that has been approved for the treatment of psoriasis arthritis and moderate to severe plaques psoriasis. Blocking PDE4 increases intracellular adenosine monophosphate levels resulting in a downregulation of proinflammatory cytokines such as IL-2, IL-5, IL-13 and increased production of the regulatory cytokine IL-10. A pilot study investigating the effect of apremilast in patients with

moderate to severe AE has demonstrated moderate improvement of skin lesions, pruritus and QoL (89), but the drug development program of apremilast for AE has been stopped.

Recommendations

Apremilast may be used in selected cases unresponsive to standard therapy for treatment of AE. (-,D)

Tofacitinib

So far only one small open label trial with the oral JAK inhibitor tofacitinib citrate has been performed in 6 patients with moderate to severe, treatment refractory AE. After 8-29 weeks of treatment they had a mean SCORAD reduction of 66 %. No adverse events were observed (90).

Recommendations

There is not enough evidence to support the use of tofacitinib in AE. (4,C)

Immunoadsorption

Immunoadsorption (IA) has been used in patients with AE and high serum-IgE levels based on the assumption that a reduction of IgE might result in a reduction of disease activity. An investigator initiated open-label pilot study in patients with severe AE recalcitrant to topical and systemic therapy showed that IA resulted in a significant decrease of SCORAD three weeks after the first cycle of 5 IA and a further improvement after the second cycle one month apart, and in parallel a reduction of skin-bound IgE (91). A recent study confirmed these results and showed long-term clinical effect of IA in AE patients (92). Another pilot study in severe AE showed a beneficial effect of immunoadsorption together with subcutaneous application of omalizumab; the serum levels of free IgE and the SCORAD decreased significantly (93).

Recommendations

Immunoadsoption might be considered for patients with severe AE and high serum IgE levels if the technology is available. (4, C)

Mast cell stabilizers

Mast cell stabilizers inhibit mast cell degranulation and thus prevent the release of histamine and other mediators. Oral cromolyn, ketotifen and pemirolast are used for asthma and other allergic diseases, but have not shown any significant effect for the treatment of AE. In the last five years, studies investigating these substances in AE have not been published.

Recommendations

Mast cell stabilizers are not recommended for the treatment of AE. (-)

Leukotriene antagonists

Montelukast is a cysteinyl-leukotriene receptor antagonist that blocks the action of LTD4, LTC4 and LTE4. It has been used at doses of 10 mg daily (5 mg/day in children below 12 years), with some reduction in SCORAD indexes (94, 95). A systematic review stated that limited evidence exists to recommend montelukast for the treatment of AE (96). Studies on leukotriene antagonist zafirlukast for the treatment of AE have not been reported in the last five years.

Recommendations

There is not enough evidence to support the use of leukotriene antagonists in AE. (2a,B)

Intravenous Immunoglobulin

Intravenous immunoglobulins (IVIG) are considered as immunomodulatory substances, but not as immunosuppressive agents. IVIG have been tried for both adults and children with severe, treatment refractory AE, but clinical trials did not indicate a high efficacy or quick onset of action despite the high cost of treatment (97, 98). IVIG may be considered as a last resort treatment in severe, treatment refractory AE in children only. It is likely that the availability of novel biologics for AE may further reduce the indication for IVIG in AE.

Recommendations

The use of IVIG in AE is not recommended. (4,D)

H1R-blocking antihistamines

Traditional histamine 1 receptor (H1R) blocking 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 (99-104). According to a Cochrane search, randomized controlled trials investigating the efficacy of antihistamine monotherapy in AE patients are lacking (105).

The first generation of sedative antihistamines such as hydroxyzine, clemastine fumarate, doxylamine, and dimetinden maleate may allow better pattern in acute situations with exacerbations of AE (evidence level D). Concerning the newer non-sedating antihistamines, studies using loratadine, cetirizine or fexofenadine demonstrated no or only a weak relief of pruritus in AE (106-108). A significant, but clinically small, antipruritic effect of fexofenadine

60 mg twice daily has been described (109). An effect on itch of a high dosage of 20 to 40 mg cetirizine daily has been observed, but this effect was primarily attributed to sedation (107).

The corticosteroid sparing effect of cetirizine in infants with severe AE has been attributed to its decreasing effect on pruritus (110). A recent study reported a beneficial effect of the non-sedating H1 antihistamine olopatadine in AE patients by decreasing nocturnal scratching without affecting sleep quality (111). Possible mechanisms of action of second generation antihistamines are a reduction of the urticarial component of AE, and blocking histamine interaction with bradykinine, downregulation of transcription factors resulting in a decrease of proinflammatory cytokine production (112).

In general, antihistamines are safe to use, also for a long period of time (113), and the major advantage seems to be relief of the symptoms of co-morbidities such as allergic asthma, rhino-conjunctivitis, urticarial dermographism and urticaria. Topical antihistamines have no effect on itch beyond that of their cooling vehicles.

H4R-blocking antihistamines

Amongst the 4 histamine receptors described in humans, the histamine 4 receptor (H4R) blocking antihistamines represent an additional promising treatment for AE (114). Clinical trials have been performed with H4R blocking agents, but the results are not published yet.

Recommendations

There is not enough evidence to support the general use of both first and second generation H1R-antihistamines for treatment of pruritus in AE. These may be tried for treatment of pruritus in AE patients, if standard treatment with TCS and emollients is not sufficient. (1b, A)

Long term use of sedative antihistamines in childhood may affect sleep quality and is therefore not recommended. (-,D)

Allergen-specific immunotherapy

Allergen-specific immunotherapy (ASIT) has been investigated for treatment of AE, the two relevant therapeutic regimens are subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT).

Introduction to allergen-specific immunotherapy for AE

Some efficacy of allergen-specific immunotherapy (ASIT) in AE has been shown in a number of case reports and smaller cohort studies (115, 116), and more recently in a larger multicenter trial with subcutaneous house dust mite immunotherapy (117). These data showed that ASIT can be used for treatment of allergic rhinitis or mild asthma also in AE patients, since the AE was obviously not worsened and sometimes even improved during or after ASIT. A few prospective studies have been performed which address the question if AE alone may be an indication for ASIT.

Even if the results of the studies are interpreted very carefully with regard to the therapeutic effects of ASIT, it is remarkable that exacerbations of the skin disease during treatment were rare, while the treatment was well tolerated in most patients. The same was true for studies in patients with coexistent AE who were treated with ASIT for respiratory atopic diseases and experienced not more often flares of eczematous skin lesions. The role of allergens in the pathophysiology of AE has been proven in controlled studies on allergen avoidance and atopy patch testing (118-120). In respiratory atopic diseases, ASIT plays an important role not only for treatment, but also for the prevention of further sensitizations and progress to more severe respiratory disease (change from rhinitis to bronchial asthma).

Hypothetically, patients with a positive atopy patch test and corresponding history of eczema flares may be candidates for ASIT with the eliciting allergen. The performed studies point to the safety of ASIT also in AE, if the treatment is performed according to the guidelines. However, the final judgement on the efficacy of ASIT in this diagnosis is still not possible due to the lack of large, controlled and randomized clinical trials with modern allergen vaccines (116).

Evidence from controlled clinical trials

Experience in a pair of monozygotic twins with AE (with spring and summer exacerbations) treated either with grass pollen ASIT or placebo in a double-blind fashion showed significant improvement and decrease of serum IgE in the patient treated with ASIT (121). Several open uncontrolled study designs also demonstrated advantages of ASIT in patients with AE, these data were often published in national or non-anglosaxon journals. Some investigators in the 1970s and 80s also showed improvement of AE in controlled trials (116).

Subcutaneous immunotherapy (SCIT)

A double-blind controlled trial of ASIT with *Dermatophagoides pteronyssinus* in children with AE failed to demonstrate superiority over placebo after a standard 8-months' course of treatment with tyrosin-adsorbed house dust mite extracts in 24 house dust mite-allergic children with AE (122). However, in a second study phase children were randomly allocated

to continue with active treatment or placebo for a further 6 months. The placebo effect was high, and the numbers were too small to permit confident conclusions, but the clinical scores suggested that prolonged ASIT may be effective with regards to several objective parameters of AE severity (122).

A small placebo-controlled study showed AE improvement in 13 of 16 ASIT treated AE patients, whereas only 4 of 10 placebo-treated AE patients improved (123). Similar results were reported for AE lesions under ASIT with house dust mite extracts (124, 125). Oral ASIT for *D. pter* was not effective in a controlled study enrolling 60 children with AE which were followed for three years (126). Conventional s.c. ASIT (n=41; 76% improved) and sublingual ASIT (SLIT; n=48; 64% improved) showed some efficacy, with adverse drug reactions occurring in 15-20% of both groups (127). A controlled study applying SLIT with house dust allergens was performed in 56 children with AE aged 5 to 16 years, but the outcome of this intervention was positive only in patients with mild to moderate AE, but not with severe AE (128).

A pilot study reported the improvement of AE together with changes in T cell subpopulations induced by IFN gamma pretreatment before ASIT with house dust mite allergens. Patients receiving placebo, IFN gamma only or ASIT only showed no treatment effect (129).

A large randomized, assessor-blinded clinical trial investigated 89 patients with AE showing a sensitization to house dust mite (CAP-FEIA $\geq$ 4) (117). Patients were injected weekly with three different doses of HDM allergen extract. With higher allergen doses, a beneficial SCORAD decrease occurred after 8 weeks compared to a control group with an “active placebo” consisting of very low allergen dose. The effect was maintained over one year and was accompanied by lower glucocorticosteroid use.

A smaller DBPC study involving 20 patients with HDM- or grass pollen sensitization also showed objective and subjective symptom relief accompanied by immunological changes under ASIT (130).

Another large, randomized double-blind placebo controlled study investigated 168 adult AE patients for 18 months. The study did not reveal efficacy in the AE patients studied, but a subgroup analysis showed statistical significance of SCORAD reduction in subgroup of severe AE patients with SCORAD > 50 (131). Longer treatment duration was associated with higher efficacy. The best outcome was observed during September to February, which may be due to the use of indoor heating and subsequent high HDM exposure.

A systematic review and meta-analysis of randomized controlled trials published until December 2012 assessed the efficacy of immunotherapy for AE. 8 randomized controlled trials that comprised a total of 385 subjects were analyzed. It has been found that ASIT has a significant positive effect on AE patients (odd ratio [OR], 5,35:95% CI, 1.61-17.77; number needed to treat 3;95% CI, 2-9). ASIT showed also significant efficacy in long-term treatment (OR, 6.42;95% CI, 1.31-7.48) for severe atopic dermatitis (OR, 3.13;95% CI, 1.31-7.48), and when administered subcutaneously (OR, 4.27;95% CI, 1.36-13.39). This meta-analysis provides moderate level evidence for the efficacy of SCIT in AE. However, these findings are based on an analysis of a small number of patients, with considerable heterogenicity among trials (132).

Sublingual immunotherapy (SLIT)

A first 18 months, placebo controlled study investigating the effects of SLIT on AE found a significant decrease of the SCORAD starting from month 9 (128).

Another study analyzed 107 patients undergoing SLIT for 12 months. A total of 84 patients finished the trial, compared to the placebo group (53,85%), the treatment group (77,78%) showed improvement in symptoms (133).

Another group of authors has investigated SLIT in AE patients allergic to HDM in a murine model (134). The mouse model induced by *Der f* allergen extract reflected the typical hallmarks of AE in humans. In the *Der f* allergens-sensitized mice, SLIT treatment with *Der f* vaccine significantly inhibited AE symptoms through correction of Th2 and Th1 cytokine predominance, therefore according to the authors SLIT could be considered as an alternative treatment for patients with extrinsic AE.

Summary of evidence

There is conflicting evidence regarding ASIT in AE, with more recent literature being more in favour of it. ASIT may have positive effects in selected, highly sensitized patients with AE. (2a)

The best evidence so far is available for ASIT with house dust mite allergens. (2a)

There is no contraindication for performing ASIT in patients with respiratory allergic diseases (allergic rhinoconjunctivitis, mild allergic bronchial asthma) and concomitant AE. (2b)

Recommendations

ASIT is currently not recommended as a general treatment option for AE. (2a, B)

ASIT may be considered for selected patients with house dust mite, birch or grass pollen sensitization, who have severe AE, and a history of clinical exacerbation after exposure to the causative allergen or a positive corresponding atopy patch test. (2a, B)

Complementary and alternative medicine in atopic eczema

There is evidence of growing interest of so-called complementary alternative medicine (CAM) as treatment for AE (135-137). CAM has been defined as “diagnosis, treatment or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine” (136). This chapter summarises available RCT-based evidence on CAM for AE.

Essential fatty acids

The most commonly used preparations in the treatment of AE are polyunsaturated fatty acids, evening primrose oil (EPO), borage oil (BO), or animal and fish oil. A systematic review published in 2016 showed conflicting results on EPO (138-141). Four smaller trials (142-145), as well as two larger trials (146, 147) and an Indian study on EPO (148) also gave conflicting results.

Negative results were obtained in a trial on eicosapentaenoic acids from Germany (149)

A study from Berlin compared the daily administration of 5,4 g docosahexaenoic acid (DHA) in 21 patients who completed the trial with an isoenergetic control of fatty acids (N=23) over 8 weeks. The SCORAD dropped significantly in the DHA group, however, significant differences to control were not observed (150).

In a comparison of dietary hempseed oil with olive oil, some parameters of skin physiology and symptoms improved under hempseed oil, but obviously without significant difference to the control group (151).

A RCT in 20 hospitalised patients with AE comparing infusions of fish oil to soybean oil revealed marked improvements within one week in both groups but a significantly greater effect in those treated with fish oil (152). Some smaller RCTs have also indicated a beneficial effect (153-155), although the largest and well reported trial did show a difference between the fish oil and the placebo (156).

EPO has also been used as topical treatment. Although a pilot study has indicated some beneficial effects (157), further studies were unable to establish a dose response relationship (158). Additional studies could not prove a beneficial effect on skin barrier function (159). Large trials on that issue, however, are lacking.

In one pilot study, the addition of gamma-linolenic acid to emollients was able to decrease elevated TEWL in atopic eczema (160).

The most recent Cochrane review on EPO and BO included 19 studies on EPO and 8 on BO (161). The authors concluded that EPO and BO lack effect on AE and that further studies would be hard to justify.

Summary of evidence

There is partly conflicting, mostly negative evidence regarding the efficacy of oral or topical applications of unsaturated fatty acids in the treatment of AE. (1a)

Recommendations

Oral application of unsaturated fatty acids is not recommended for treatment of AE. (1a, A)

Topical application of unsaturated fatty acids as an ingredient in emollients may be tried in selected cases. (D,-)

Phytotherapy

Detailed background information on herbal therapy in dermatology is published (162). Two RCTs investigated the efficacy and safety of topical chamomile preparation (163) and a hypericum extract cream for AE (164).

The chamomile cream was moderately superior to 0.5% hydrocortisone cream regarding pruritus, erythema and desquamation, but not different to the vehicle cream. The cream containing hypericum extract standardized to 1.5% hyperforin was compared to the corresponding vehicle cream in a half side comparison in 18 patients with mild to moderate AE. The modified SCORAD index improved over 4 weeks with both therapies, but the improvement was significantly higher under active treatment. A further study compared a topical preparation of Mahonia aquifolium, Viola tricolor and Centella asiatica with the vehicle cream in 88 patients and could not find significant differences (165). A subgroup analysis revealed superiority of the plant preparation under dry and cool weather conditions.

Plant extracts are well known to induce contact sensitisation and subsequent contact allergy (166, 167). It was demonstrated that so called “phytocosmetic creams” containing a mixture of plant extracts may also contain triamcinolone acetonide as an active ingredient (168).

The concerns regarding side effects of phytotherapy with crude plant extracts must not be generalized to emollients containing protein free oat plantlet extracts (169, 170). (see section “Emollients plus” in chapter “Basic therapy”).

Summary of evidence

Beside many negative results, there is only one small RCT indicating a beneficial effect of hypericum cream as a topical phytotherapy. (1b)

Topical use of crude plant extracts may cause contact sensitization and contact dermatitis. (1a, A)

Recommendations

Topical use of crude plant extracts is not recommended for treatment of AE. (1b, C)

Chinese herbal medicine (CHM)

Chinese herbs are part of the traditional Chinese medicine which consists of Chinese herbs administered orally or topically, acupuncture, diet and exercise (171, 172). CHM is promoted as treatment for AE, taken orally as decoction, usually consisting of about 10 different herbs. The first positive RCTs of CHM in the treatment of AE outside China were published by Sheehan in 1992 (173). Serious adverse effects including fatal hepatitis have been reported by independent investigators following these trials (171, 174-176). Further trials on

Zemaphyte®, a commercial product of Chinese herbs, revealed conflicting results (177, 178).

The oral application of a combination of *Eleutherococcus, Achillea millefolium*, and *Lamium album* was not superior to placebo after two weeks (179).

The most recent Cochrane review on CHM included 28 studies encompassing 2306 patients (180). When compared to placebo CHM showed higher clinical effectiveness (RR 2.09, 95% CI 1.32 to 3.32) in 2 studies. The total effectiveness rate in CHM groups was found to be superior (RR 1.43, 95% CI 1.27 to 1.61) when compared to conventional therapy in 21 studies. The authors assessed most studies at high risk of bias and found substantial inconsistency between studies. Therefore it was concluded that there is no conclusive evidence that CHM could reduce the severity of AE. A similar result was achieved by the systematic review of Tan and co-workers (181). The most recent RCT showed significant effects of CHM on SCORAD and QoL scores when compared to the placebo group (182).

Summary of evidence

There is no conclusive evidence to support the use of Chinese herbs in the treatment of AE. (1a)

Recommendations

The use of Chinese herbs is not recommended for treatment of AE. (1a, A)

Acupuncture/Acupressure

Acupuncture has been studied considering allergen-induced itch as primary endpoint but not systematically or within randomised controlled trials as a treatment for AE. Case series of patients including those with AE indicate some beneficial effects but studies implying a rigorous methodology are needed (183-186). There is initial evidence from a small pilot trial that acupressure might be helpful in reducing pruritus and lichenification in AE patients (187).

Summary of evidence

There is absence of evidence to support the use of acupuncture or acupressure in the treatment of AE. (-)

Recommendations

The use of acupuncture or acupressure is not recommended for treatment of AE. (-, D)

Autologous blood therapy

One RCT compared the intramuscular re-injection of 1 to 3 ml autologous blood over 5 weeks to the injection of the equivalent amount of sterile saline solution (188). Patients were recruited via press advertisement and finally 30 subjects participated. Over a 9 weeks period, AE severity measured by SASSAD dropped significantly in the verum group from 23.2 to 10.4 and did not change in the placebo group (21.0 to 22.5). Significant differences were not observed in health related quality of life and the subjective assessment of pruritus

skin appearance and sleep quality. The data suggest a beneficial effect of autologous blood therapy with respect to the signs score. This finding should be confirmed in larger trials and different settings.

Summary of evidence

There is very limited evidence supporting the use of autologous blood therapy in the treatment of AE. (2b)

Recommendations

The use of autologous blood therapy is not recommended for the treatment of AE. (2b, B)

Bioresonance

One RCT has been published so far, comparing bioresonance with a sham (inactive pseudo-) procedure in 36 children with AE attending a specialized rehabilitation unit in Davos, Switzerland (189). After 4 weeks, AE severity had improved in both groups with slight superiority of the active group but without statistical significance. Further studies under more usual outpatient conditions are needed.

Summary of evidence

Current evidence from a single trial does not indicate a substantial clinical effect of bioresonance for treatment of AE. (2b)

Recommendations

The use of bioresonance for treatment of AE is not recommended. (2b, B)

Homoeopathy

Homeopathy is a system of alternative medicine created in 1796 by Samuel Hahnemann, based on his doctrine of like cures like. Large case series illustrating the therapeutic benefits of homeopathy have been published as papers or books (190, 191). A recent uncontrolled trial of 17 patients with longstanding AE in Japan revealed a marked improvement after the introduction of homoeopathic treatment (192). A classical randomised placebo controlled trial was initiated in Germany including 60 patients (193), showing no difference between placebo and verum homeopathy in the outcome of AE (194).

Summary of evidence

There is absence of evidence to support the use of homeopathy in the treatment of AE. (2b)

Recommendations

The use of homeopathy is not recommended for treatment of AE. (2b, B)

Massage therapy / aroma therapy

The effect of additional massage therapy for AE, applied daily for 20 minutes over a one month period compared to standard therapy alone, was investigated in a randomised trial in

20 children (195). Greater degrees of improvement in anxiety scores, tactile defensiveness and coping index were reported by parents of children in the active group. Furthermore clinical signs such as scaling and excoriation improved significantly in the massage group. Appropriate statistical comparisons between groups, however, were not performed. A further small cross-over trial in 8 children compared massage with essential oils (aroma therapy) to conventional massage (196). Both treatment groups improved significantly without significant differences between groups. Given the small sample size, conclusions on the beneficial effects of additional aroma therapy cannot be drawn.

Summary of evidence

There is insufficient evidence to support the use of massage / aroma therapy in the treatment of AE. (4)

Recommendations

The use of massage / aroma therapy is not recommended for treatment of AE. (4, C)

Salt baths and thermal spring water balneotherapy

Salt bath has been used for a long time to control chronic inflammatory skin diseases, especially psoriasis. Based on this experience and anecdotal evidence, salt was recently recommended also in the treatment of AE. The efficacy of salt bath alone, however, has not been studied systematically in AE. In the current reports, salt baths were investigated as part of a complex climatotherapy or in combination with UV-therapy (197-204). From these studies it cannot be concluded that salt baths provide a consistent and significant clinical effect on AE. Conventional balneotherapy with or without synchronous UV therapy has been shown to be effective in AE but was not considered as CAM in this chapter. Balneotherapy with thermal spring water has been shown to be beneficial in children with mild to moderate AE with an effect similar to mid-potency topical corticosteroids (205).

Summary of evidence

There is insufficient evidence to support the use of salt baths in the treatment of AE. (4)

Cohort studies indicate that thermal spring water balneotherapy with or without phototherapy may be effective in mild to moderate AE (2a, 2b)

Recommendations

The use of salt baths is not generally recommended for treatment of AE. (4, C)

Thermal spring water balneotherapy may be considered in mild to moderate AE (B, 2a, 2b)

Vitamins and minerals

A total of 6 trials were identified investigating vitamins or minerals in the treatment of AE (206-211). A placebo-controlled study from Italy studied oral vitamin E (400 IU) in 96 patients (210). Greater clinical improvement was reported for the vitamin E group but without

results of statistical tests. Similarly, a smaller study of 49 patients comparing vitamin E plus vitamin B2 to vitamin E or vitamin B2 alone revealed a superiority of the combination treatment with respect to the physician's assessed overall usefulness and global rating (208). A further trial in 60 adults with AE compared selenium or selenium plus vitamin E vs. placebo over a 12 weeks period (207). The AE severity score fell in all 3 study arms without significant differences. A Hungarian study compared multi-vitamin supplementation in 2090 pregnancies to trace element supplementation in 2032 pregnancies over a 17 month period (206). AE occurred more frequently in the multi-vitamin group (0.7% vs. 0.2%). Although this unexpected result could be a chance finding as suggested by the authors, detailed studies in the prospective setting are needed. A small trial has investigated the zinc supplementation vs. placebo in 15 children over a 2 month period (212). The severity score increased in both study groups without significant differences. There is one published RCT comparing pyridoxine (vitamin B_6) vs. placebo in 41 children over a 4 weeks period (209). The median severity score increased in the pyridoxine group whereas an improvement was observed in the placebo group. None of the differences were statistically significant.

Following a pilot study on vitamin D (211) more RCTs on that subject were published recently. Thereby vitamin D supplementation showed statistically significant improvement in clinical scores in 20 i.e. 60 adults (213, 214) and 107 children (215), whereas another trial in 60 adults failed to prove significant effects by vitamin D supplementation (216). Vitamin D supplementation of mothers during lactation did also not improve facial eczema in 164 children studied (217). A further RCT in 45 adults patient showed equal and significant reduction of the SCORAD score by vitamin D or E supplementation (34.8%, 35.7% resp.) and an even higher reduction by the combination of both vitamins (64.3%) (218).

Summary of evidence

There is preliminary evidence that vitamins, especially vitamin E and D, may be useful in the treatment of AE. (1b)

Recommendations

There is not enough evidence to recommend vitamin supplementation for routine use in AE patients. (2b, B)

Topical Vitamin B12 in avocado oil

There are two smaller studies with half-side comparisons, which indicate a mild beneficial effect of a preparation containing 0.07% vitamin B12 in avocado oil compared to a placebo preparation (219, 220).

Summary of evidence

There is preliminary evidence that a topical preparation of Vitamin B12 in avocado oil may be useful in the treatment of AE. (2b)

Recommendations

There is not enough evidence to recommend topical preparations of Vitamin B12 in avocado oil for routine use in AE. (2b, B)

Harms of CAM

Contrary to widespread assumptions of the public, CAM is not free of side effects. Dietary regimens involving strong restrictions can lead to harmful sequels in terms of malnourishment. Therapeutic procedures involving organic material from plants or animals can be associated with severe toxic or allergic reactions. Finally, patient's and parent's adherence to assumingly effective CAM may delay or hinder a severely affected patient's access to effective or even lifesaving therapy.

Psychosomatic counseling

Psychological and emotional factors influence the clinical course of AE, which is mirrored in the German term “neurodermitis”. Interventions including patient education, eczema action plans, and a quick return for a follow-up visit improve adherence (221). The reason for treatment failure in more than one-half of patients referred to specialist centers is that the treatment is not being administered. Doctors often have insufficient time to educate patients and their caregivers about the correct application of ointments and creams, and this adversely affects compliance. Many countries have patient organizations and support groups that provide useful supplementary literature (222).

Poor adherence to treatment

Poor adherence to treatment is a major factor limiting treatment outcomes (223), and may have different causes: *Stress* can elicit severe exacerbations of eczematous skin lesions (224-226). The *itch-scratch cycle* is especially vulnerable to psychological influences and can show a tendency to self-perpetuation (227-229). *Psychosomatic disease* in the sense of anxiety or depression can be a co-morbidity of AE (228, 230). *Intrafamiliar psychodynamics* are also well-known factors influencing the clinical course of AE (231, 232).

Educational interventions

A Cochrane review analyzed ten RCTs of psychological or educational interventions, in addition to conventional therapy, for AE in children (233). One study of a psychological intervention used biofeedback and hypnotherapy as relaxation techniques versus discussion only. Three of the four educational studies identified significant improvements in disease severity in the intervention groups. The fourth trial evaluated long-term outcomes and found a statistically significant improvement ($P < 0.01$) in disease severity and parental quality of life over 12 months in all studied age groups (three months to 18 years). Heterogeneity in outcome measures and inadequate methodology limited data synthesis in this review. The psychological and educational interventions were delivered by nurses or multidisciplinary teams (234). Quality of life (QoL) is severely impaired in AE patients (235), as shown in a recent review: Statistically significant improvements in QoL of AE patients by patient education were reported in five studies, whereas the severity of skin disease improved significantly in three studies out of ten studies evaluated. In conclusion, patient education appears to be effective in improving QoL and in reducing the perceived severity of skin disease (236-238). (See chapter: Educational interventions for AE)

Psychotherapeutic approaches

Most psychological training programs include relaxation techniques (239), habit training for social competence and communication as well as coping behavior and improvement of self-control with regard to disrupting the itch-scratch cycle.

Psychosomatic counseling: Randomized controlled trials compared the use of topical corticosteroid alone with steroids together with a behavioral therapy program which led to a significantly pronounced improvement of skin condition and itch-scratch behavior (240).

Behavioral therapy: Behavioral therapy against itch was studied, showing a significant improvement in symptoms after one year (241-243). Especially habit reversal techniques improve itch in atopic dermatitis (244).

Autogenic training: Together with cognitive behavioral therapy was studied in a standardized educational program (see chapter “Education”) (245).

Relaxation: Relaxation methods may be more effective in reducing disease severity than discussion only (246).

Parents who had negative treatment experiences in the past and possessed only poor coping abilities with regard to scratch control benefitted the most from the training program. The outcome of the education measure was independent of parents' schooling, vocational level and income (247). Another publication stated that there is currently only limited research evidence on the effect of educational and psychological approaches when used alongside medicines for the treatment of childhood eczema (233). It is well possible that there is limited research activity in this area of intervention, thus providing limited evidence of the measurable effects of interventions.

Summary of evidence

Psychosomatic counseling can be a helpful adjuvant procedure in the management of patients with AE including psychotherapeutical approaches and behavioral therapy techniques. (3b)

Relaxation techniques may cause significant improvements in disease severity. (1a)

Individual psychotherapeutic approaches can be helpful in individual patients. (-)

Psychological and psychosomatic interventions are an essential and helpful part of educational programs. (1a)

Recommendations

Psychosomatic counseling, psychotherapeutical approaches, behavioural therapy techniques, autogenic training, relaxation techniques, psychological and psychosomatic interventions are recommended in selected patients. (1a, A)

The indication should be confirmed by specialists in the field of psychodermatology. (-, D)

Educational interventions for atopic eczema

Adherence to treatment and poor quality of life (QoL) are key issues in patients with AE (248). Patient education (PE) interventions can help patients and their families to better understand their disease and cope with treatment in order to maintain or even improve QoL and treatment adherence. The aim of PE is not simply to provide information by leaflets in the waiting rooms, but entails the transfer of skills (e.g. self- management of the disease, treatment adaptation) from a trained healthcare professional to the patient or their parents. Additionally, PE should aim to reduce doctor's visits, facilitate a better partnership between the doctor and the patient/parents and restore family dynamics. PE should also lead to a decrease of the long-term costs of AE treatment. A recent study showed that parents with negative treatment experiences in the past and poor coping abilities regarding scratch control benefitted most from PE programs (247).

High-quality PE programs should ideally be evidence-based, tailored to a patient's individual educational and cultural background (rather than being standardized in form and content), and have well-defined content and activities (233, 236, 249).

Educational service delivery models

There are different types of PE programs running all around the world. These differ in number and certification of the educators, number of participants, age of patients, teaching techniques, duration and frequency of interventions (233, 250). Thus, because the content of the PE programs varies greatly, comparison between studies is difficult. For example, while the intervention by Staab (237) entailed 2-h sessions, involving a trained multidisciplinary team, once a week for 6 weeks, the intervention by Shaw et al (251) involved a trained medical student running a single 15-min session. Most of the published intervention programs are structured as follows:

Multidisciplinary age related structured group training educational programs (eczema school): There is evidence that structured age related programs are significantly improving severity score, improving coping behavior, parents handling their affected children and increasing disease knowledge. (237, 241, 252-255). A recent multidisciplinary eczema school program tailored to the adult situation showed also high efficacy (238).

Eczema workshops: Eczema workshops may improve the disease severity of patients with AE (256, 257). There is also a greater adherence to eczema management (coping behavior, parent's handling their affected children) in the eczema school, compared with the standard dermatologist-led clinic (254).

Nurse-led eczema workshop: There is evidence that the benefits of nurse interventions are the reduction in the severity of the condition and the better use of topical therapies. There is a reduction in referrals to general practitioners or dermatologists, disease knowledge and self-management techniques are improving (254, 256, 258, 259). The relative effectiveness of nurse led programs compared to multidisciplinary age related, structured programs is unclear.

Structured lay-led self-management education training programs: They lead to a small statistically-significant reduction in disease status (pain/ itch, disability, fatigue) and a small, statistically-significant improvement in depression and psychological well-being but there was no difference in quality of life (260). There is no evidence that such programs improve psychological health (261, 262).

E-health during follow-up of patients with AE

E-health intervention follows the initial diagnosis and treatment with face-to-face contact. This is just as effective as usual face-to-face care with regard to quality of life and severity of disease. However, when costs are considered, e-health is likely to result in substantial cost savings. Therefore, e-health is a valuable service for patients with AE. (263, 264).

Forms of educational intervention tools

Depending of cultural backgrounds and health care systems, a wide variety of tools are used in PE programs (practical demonstrations sessions as florescent cream advices (265), written action plans (266), lectures, question and answer sessions, leaflets, online videos etc.) but there is no evidence that a specific tool is more efficient than another (233).

Summary of evidence

PE programs for AE in children and adults are efficient and established already in many countries. The multidisciplinary age related structured group training educational programs (eczema school) have the most evidence-based benefit. (1a)

Eczema workshops lead to an improvement in severity scores, there is greater adherence in eczema-management, itch-scratching cognition, and there is additional psychological benefit. (2a, 2b)

Nurse led programs result in more effective use of topical therapies. (3b)

Nurse led programs result in an improvement of severity scores. (2a)

Nurse led programs may be sparing doctor's time. (2b)

There is some evidence that a direct-access, online model for follow-up dermatologic care is equivalent to classical in-person care for patients with AE. (2a)

There is no evidence of change in severity scores due to lay-led self-management education programs, which have weak effect in improvement although the disease knowledge is increasing (-)

Recommendations

PE programs for AE in children and adults are recommended as an adjunct to conventional therapy of AE. (1a, A)

Conclusion and Outlook

The complex pathophysiology of AE explains why the therapeutic strategies also comprise multiple aspects and are complex in nature. Although there is a strong genetic preposition, patients with AE must not be desperate. Labelling AE as “incurable” is not correct, since the eczema with its symptoms can very well be treated and may disappear totally. Adequate treatment needs the cooperation of the well-informed patient with the physician and time; educational programs are extremely helpful.

In the recent past, new medications resulting from immunological research have been licensed for AE. The appearance of biologics specific for immune mediators and receptors are extremely promising and will be available soon for patients in many European countries and the rest of the world.

Tables

Table 1 Grades of evidence

1a) Meta-analysis of randomized clinical trials (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
Recommendations (see Table 2) were classified based on the grade of evidence.

Table 2 Classification of strength of recommendation

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

Table 3 Language of recommendations

Wording in standard situations	**Free text explanation**
must be used	This intervention should be done in all patients, unless there is a real good reason not to do it
should be used	Most expert physicians would do it this way, but some would prefer other possible action
may be used	It would be correct to do this intervention, but it would also be correct not to do it; the choice depends largely on the specific situation
is possible	Most expert physicians would do something else, but it would not be wrong to do it
may be used in selected patients only	This intervention is not adequate for most patients, but for some patients there may be a reason to do it
is not recommended	Most expert physicians would not choose this intervention, but some specific situation may justify its use
must not be used	This intervention is inadequate in most situations

Table 4: Systemic drugs for treatment of severe atopic eczema

	cyclosporine	methotrexate	azathioprine	mycophenolic acid	corticosteroids	dupilumab
overall recommendation	++ acute flare intervention	++ long term maintenance	can be used long term	++ little toxicity	outdated♦	long term maintenance
time to respond (weeks) #	2	8-12	8-12	8-12	1-2	4-6
time to relapse (weeks)	< 2	> 12	>12	> 12	< 2	> 8
most important side effects	serum creatinine ↑ blood pressure ↑	hematological liver enzymes gastro-intestinal	hematological ↑ liver enzymes ↑ gastro-intestinal	hematological skin infections gastro-intestinal	Cushing's osteoporosis diabetes	conjunctivitis
starting dose adult	4-5 mg/kg/day ♦	5-15 mg/week	50 mg/day ♦	MMF 1-2 g/day (EC-MPA 1.44 g/day)	0.2-0.5 mg/kg/day	600 mg loading dose
maintenance dose adult	2.5-3 mg/kg/day	most often 15/week; can increase to max 25 mg/week	2-3 mg/kg/day*	MMF 2-3 g/day** (EC-MPA 1.44 g/day)	not for maintenance♦	300 mg/ 2 weeks
starting dose children	5 mg/kg/day	10–15 mg/m^2/week	25-50 mg/day	MMF 20–50 mg/kg/day	0.2-0.5 mg/kg/day	no data yet
maintenance dose children	2.5-3 mg/kg/day	increase 2.5-5mg/week, decrease 2.5mg/week to effective/lowest effective dose	2-3 mg/kg/day*	increase daily total dose by 500 mg every 2–4 weeks up to 30-50 mg/kg/day	not for maintenance♦	no data yet
pregnancy	possible	teratogenic, absolutely contra-indicated	conflicting data, possible with strict indication	teratogenic, absolutely contra-indicated	possible	no data yet

fathering	possible	little information, conflicting data, contra-indicated	little information, possible with strict indication	conflicting data	possible	no data yet

* TPMT heterozygote 1-1.5 mg/kg/day ♦ see full text # time to reach most of expected full response

MMF: mycophenolate mofetil; EC-MPS: enteric-coated mycophenolic sodium

Table 5: Upcoming systemic drugs for treatment of atopic eczema

	Substance code	Target	Substance class	Development phase	Registration status	Trial data	Adverse drug effect signals	Recommendation
Nemolizumab	CD-14152 (formerly CIM-331)	IL31R alpha	IL31 blocker	III		♦	peripheral edema?	
Tralokinumab	CAT-354	IL13	Th2 blocker	III				
Lebrikizumab	TNX-650	IL13	Th2 blocker	II				
Tezepelumab	MEDI-9929	TSLP	TSLP blocker	II				
Upadacitinib	ABT-494	JAK1	JAK inhibitor	II				
	PF-04965842	JAK1	JAK inhibitor	III				
	ZPL-389 (formerly PF-03893787)	H4R	H4R blocker	II				

♦ see full text

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