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GUIDELINES

Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I

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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 into 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.

Conflicts of interest

A. Wollenberg has been an advisor, speaker or investigator for ALK-Abelló, Almirall, Anacor, Astellas, Beiersdorf, Bencard, Bioderma, Chugai, Galderma, Glaxo SmithKline, Hans Karrer, Leo Pharma, L'Oreal, Maruho, MedImmune, Novartis, Pfizer, Pierre Fabre, Regeneron and Sanofi. S.Barbarot has been an advisor, speaker or investigator for Bioderma, La Roche-Posay, Sanofi-Genzyme, Novalac, Ferring, Abbvie, Novartis and Janssen. T. Bieber has been advisor, speaker or investigator for Abbvie, Allmirall, Anacor, Astellas, Bayer, Celgene, Chugai, Daiichi-Sankyo, Galderma, Glaxo SmithKline, Leo Pharma, Novartis, Pfizer, Pfizer, Pierre Fabre, L'Oréal, La Roche-Posay, Regeneron and Sanofi. S. Christen-Zaech has been an advisor, speaker or investigator for Galderma, L'Oreal, La Roche-Posey, Pierre Fabre, Permamed, Procter and Gamble, and Sanofi-Genzyme. M. Deleuran has been an advisor, speaker or investigator for AbbVie, Leo Pharma, MEDA, Pierre Fabre, L'Oréal, La Roche-Posay, Pfizer, Regeneron and Sanofi. A. Fink-Wagner has been working with or an advisor or speaker for ALTANA, Novartis, Nycomed, Hoffmann-La Roche and Teva. U. Gieler has been an advisor or speaker for Allmirall, Astellas, Bayer, Celgene, Galderma, Glaxo SmithKline, Leo Pharma, Lilly, Novartis, Pfizer, Pierre Fabre, La Roche-Posay and Sanofi -Aventis. G. Girolomoni has been an advisor, speaker or investigator for AbbVie, Abiogen, Allmirall, Amgen, Bayer, Biogen, Boehringer Ingelheim, Celgene, Eli Lilly, Galderma, Hospira, Janssen, Leo Pharma, Menlo therapeutics, Merck, MSD, Mundipharma, Novartis, Otsuka, Pfizer, Pierre Fabre, Regeneron, Sandoz, Sanofi and Sun Pharma. S. Lau has received grants from Allergopharma and Symbiopharm and an honorarium from Merck as member of a drug monitoring committee and ALK and DBV Technologies. A. Muraro has been a speaker for Meda, Nestlè and Stallergenes. M. Czarnecka-Operacz has been an advisor, speaker or investigator for Allergopharma, Allmiral, Bioderma, Berlin Chemie, Mennarini, Novartis, Pierre Fabre, Galderma, Janssen and Leo Pharma. T. Schäfer has been a speaker for Abbott, Bencard, Dr Pfleger, Norvatis and Syneron-Candela. P. Schmid-Grendelmeier has been an advisor or speaker for ALK-Abello, Allergopharma, La Roche-Posay, MEDA, Novartis, Sanofi and Stallergenes. D. Simon has been an advisor, speaker or investigator for Roche, Novartis, Galderma, Glaxo SmithKline, Merz Pharma (Schweiz), Almirall, Sanofi and Eli Lilly. Z. Szalai has been an advisor for Pfizer, speaker or investigator for Bayer, Novartis, Pierre Fabre, Sanofi and Leo Pharma. J.C. Szepietowski has been a consultant and advisor for AbbVie, Celgene, Dignity Sciences, Leo Pharma, Novartis, Pierre Fabre and Sandoz; investigator for AbbVie, Actelion, Amgen, GSK, Janssen, Merck, Novartis, Regereron, Takeda and Trevi; speaker for AbbVie, Actavis, Astellas, Janssen, Leo Pharma, Novartis, SunFarm, Sandoz and Eli Lilly. A. Taïeb has been an advisor for Anacor, Bioderma, Chugai, Galderma, Roche and Pierre Fabre. A. Torrelo has been an advisor, speaker or investigator for AbbVie, Anacor, Astellas, Bayer, Beiersdorf AG, Galderma, Meda, Novartis and Pierre Fabre. T. Werfel has received support for research projects from AbbVie, Astellas, Janssen/JNJ, Meda, Regeneron/Sanofi, Takeda and Ziarco, and has been an advisor for AbbVie, Allmiral, Leo Pharma, Lilly, MSD, Novartis, Regeneron/Sanofi, Roche, Stallergen and Ziarco. J. Ring has been an advisor, speaker or investigator for ALLERGIKA, ALK-Abello, Almirall-Hermal, Anacor, Astellas, Bencard/Allergy Therapeutics, Galderma, GSK-Stiefel, Leo Pharma, Meda, MSD, Novartis, Phadia-ThermoFisher and Sanofi.

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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-y: 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: mycophenolate mofetil
MTX: methotrexate
mTLSS: modified Total Lesion Symptom Score
NB-UVB: narrowband 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-sign 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

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).

Although several diagnostic criteria have been proposed over time, the classical Hanifin and 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 based on a single global assessment by the investigator only. The HOME group is an initiative of methodologists, industry representatives, patients 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, although it has an additional strong focus on evidence from the literature. Consensus was achieved among the nominated members of the European interdisciplinary expert group (Fig. 1).

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]

Database 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 S1, Supporting Information). 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, although 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 and Tables (see Tables 4 and 5) 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, paediatricians, 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. Healthcare 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, to 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, as many patients cannot overlook the therapeutic options, even if they have access to transparent guidelines.

(a) 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 immunosuppression: cyclosporine 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 glucocorticosteroids 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)

(b) 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 immunosuppression: cyclosporine 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 glucocorticosteroids class II [2] or depending on local cofactors: topical calcineurin inhibitors [2], antiseptics incl. silver, silver coated textiles
BASELINE: **Basic therapy**	Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests)

Figure 1 Treatment recommendation for adults (a) and children (b) with atopic eczema.

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

Patients and caregivers should actively be involved in therapeutic decisions at all stages 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 programme, eczema school').

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	Skin atrophy	Initial burning/stinging	Initial burning/stinging
	Telangiectasia	Telangiectasia		
	Striae distensae	Striae distensae		
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	Phosphodiesterase 4	PDE4 blocker	IV	App. USA[†]	More effective than vehicle, no comparative study	Application site pain	
	OPA-15406	Phosphodiesterase 4	PDE4 blocker					
	E6005	Phosphodiesterase 4	PDE4 blocker					

[†]See full text.
PDE, phosphodiesterase; app, approved.

Negative effects of air pollutants upon the development and maintenance of AE, such as 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 aeroallergens in patients with AE.[14]

Exposure to traffic exhaust has been shown to be associated with an increased risk to develop AE in preschool children.[15,16] Moreover, diesel exhaust particles may favour 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 between smoking and AE in adolescents and adults in all continents of the earth.[20] It remains unclear, however, whether smoking is a provocation factor in AE or whether 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 ecosystem 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 favour of house dust mite avoidance in established AE.[27] Rehabilitation programmes 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 preschool 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 future.[39]

Clothing and textiles – contact allergens
Smooth clothing and avoidance of irritating fabrics and fibres are 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 causes of contact allergy to cosmetics.[41]

Occupational aspects
Special recommendations must be given in individual counselling programmes 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, as 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 transepidermal water loss leading to epidermal microfissuring. 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 superinfection. 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 min) 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 bathwater is an additional option for the 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 the 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 two.[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 bathwater may be useful for the 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 has 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 restricts 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, increases 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 and kidney dysfunction in infants and should be avoided in this age group, whereas 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 of 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 licence as a topical drug. These products may contain, for example, saponins, flavonoids and riboflavins from protein-free oat plantlet extracts, or bacterial lysates from *Aquaphilus dolomiae* or *Vitreoscilla filiformis*.[61] These lysates 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

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.

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 wintertime (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, soya, 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 h after the administration of the allergen, with skin manifestations such as urticaria, angio-oedema,

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 6–10 h 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 6–48 h 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 hyporeactivity, eczema at the test site, lack of compliance for SPT in infancy). 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 soya allergy).

Atopy patch test (APT) is performed with self-made food material using a 1/10 dilution in saline of the fresh food applied for 24–48 h 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 h or 48 h

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 randomized 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 dropout 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, has 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 such as *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 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 probiotics 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 to 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 superpotent (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. Superpotent TCS (group IV) are not recommended for AE treatment, especially not in children.[3] Potent and very potent corticosteroids of groups III and IV are more likely to cause depression of adrenal function than group I and group 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). Children should be treated with less potent TCS than adults. 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 telangiectasias (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 reviewed.[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 with 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 paediatric patients with severe AE, the efficacy and safety profile of pimecrolimus cream 1% combined with fluticasone were similar to those 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 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 study and a 5-year pimecrolimus study.[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 of 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

Topical calcineurin inhibitors 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)

Topical calcineurin inhibitors 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 TCI should be considered. (-, D)
- TCI 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 the 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 with 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 programme 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% vs. 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 and 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, IL-13 and IL-31 has been observed under UVA1 therapy.[169] Induction of apoptosis of T helper cells most probably is 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 in ICAM1 expression on keratinocytes has been observed and further enhanced via IL-10-induced reduction in 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 of 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 centres for the 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 in non-melanoma skin cancer with NB-UVB and UVA1.[185,186] The benefit/risk ratio of medium- and high-dose UVA1 (>20–70 J/cm^2) 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 are 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
Narrowband UVB has a better safety and efficacy profile compared to broadband UVB. (1a)

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

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

All UV treatments pose theoretically a long-term risk of development of skin ageing 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 narrowband UVB are recommended for the treatment of AE in adult patients. (1b, A)
- Narrowband UVB is preferred over broadband 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 the treatment of AE patients. (-,D)
- Although phototherapy is rarely used in prepubertal children, it is not contraindicated; its use depends rather on feasibility and equipment (NB-UVB). (-,D)

Antipruritic 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 counselling').

Topical therapy

Glucocorticosteroids Topical corticosteroids have anti-inflammatory activity rather than acting as direct antipruritic 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 six RCT with topical corticosteroids (desonide hydrogel 0.05%, clobetasol 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 with 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 in both adults and children. Twenty-two 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 three 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 with 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-palmitoylethanolamine was used in a multicentre, large cohort, open-label study as adjuvant treatment in AE.[74] A total of 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 crossover trial was performed with topical μ-opioid receptor antagonist nalmefene. The drug was used during two 7-day periods separated by the washout 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.

Anaesthetics 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-fibres. 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-palmitoylethanolamine 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 narrowband UVB and UVA1 as the most effective in the treatment of AE, including reduction in 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. Narrowband 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 with 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 paediatric 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 randomized controlled studies in AE. A dosage of 10 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 the treatment of AE itch.

Selective serotonin reuptake inhibitors The antipruritic effect of the selective serotonin reuptake inhibitors paroxetine and fluvoxamine 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 in 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 the 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, diarrhoea, 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 the treatment of pruritus in AE. These may be tried for the 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)

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Assignment of guideline sections to draft authors.
Table S2. Members of the guideline panels (role in the guidelines development, discipline, institution)