



European Dermatology Forum

Guideline on the Treatment of Atopic Eczema (Atopic Dermatitis)

Developed by the Guideline Subcommittee "Atopic Eczema" of the
European Dermatology Forum

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Conflicts of interests

Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis)					
		Taieb	Fink-Wagner	Gieler/Fabre	Szalai
1	Grant	-	-	Atopic Dermatitis Education Programme (Schnupperschulung Deutschland)	-
2	Consulting fee or honorarium	-	From EFA	-	-
3	Support for travel to meetings for the study or other purposes	-	From EFA	Yes 3 meetings	-
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	-	From EFA	-	-
5	Payment for writing or reviewing the manuscript	-	From EFA	-	-
6	Provision of writing assistance, medicines, equipment, or administrative support	-	-	-	-
7	Other	-	-	-	-

This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work NONE					
1	Board membership	JACFR Pediatric board Abbott	GAAPP	Almirall Skin Academy	-
2	Consultancy	Galderma, Pierre Fabre	GAAPP and Pharmaxis	Abott	Pfizer, Unilever
3	Employment	-	-	-	-
4	Expert testimony	-	-	-	-
5	Grants/grants pending	-	-	LOEWE Study Government of Health Hessen	-
6	Payment for lectures including service on speakers bureaus	Several for Atopic Dermatitis and Psoriasis not Vitiligo (Galderma, Intendis, Astellas)	-	About 10	Johnson and Johnson
7	Payment for manuscript	-	-	-	-

	preparation				
8	Patents (planned, pending or issued)	Issued Propranolol for hemangiomas 2011CEuropean patent	Yes for ALTANA Pharma beginning of the new century, when I was employed there	-	-
9	Royalties	-	-	-	-
10	Payment for development of educational presentations	Astellas (AD Workshop 2011)	-	-	Astellas, Leo Pharma, MSD
11	Stock/stock options	-	ALTANA	-	-
12	Travel/accommodations/meeting expenses unrelated to activities listed**	EADV and JDP meeting, Schering Plough, Astellas, Bioderma	Byk Gulden, Altana Nycomed	Novartis 1 meeting	Astellas
13	Other (err on the side of full disclosure)	-	-	-	-

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Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	-	I do not think so, however, I were used to work for the International Red Cross and the Malteser	-	Clinical studies with Pierre-Fabre, Abbott

Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis)					
		U. Darsow	Ständer	Seidenari	Deleuran
1	Grant	-	-	-	-
2	Consulting fee or honorarium	-	-	-	-
3	Support for travel to meetings for the study or other purposes	-	GSK	-	-
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	-	-	-	-
5	Payment for writing or reviewing the manuscript	-	-	-	-
6	Provision of writing assistance, medicines, equipment, or administrative support	-	-	-	-
7	Other	-	-	-	-

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Relevant financial activities outside the submitted work					
1	Board membership	-	-	-	Astellas Pharma
2	Consultancy	-	Astra Seneca, Beiersdorf AG, Kyorin, Dr. Suwelack, Leo, Maruho, MSD, P&M Cosmetics, Pierre Fabre, Nerre, Sanofi Aventis, Serentis, Wolff	-	Leo Pharma Merck
3	Employment	-	-	-	-
4	Expert testimony	-	-	-	-
5	Grants/grants pending	-	-	-	-
6	Payment for lectures including service on speakers bureaus	-	Aesca Pharma, Almirall/Hermal, Astellas Pharma, Basilea, Beiersdorf AG, Birken, Essex Pharma, GSK, Pierre Fabre, Maruho, 3M Medica, Mundipharma, Novartis Pharma, Serono	Payments for lectures during dermoscopy courses	-

7	Payment for manuscript preparation	-	-	-	-
8	Patents (planned, pending or issued)	-	-	Private patients	-
9	Royalties	-	-	-	-
10	Payment for development of educational presentations	-	-	Payment from the Municipality of Modena for courses	-
11	Stock/stock options	-	-	-	-
12	Travel/accommodations/meeting expenses unrelated to activities listed**	-	-	Congress accommodations	Pfizer
13	Other (err on the side of full disclosure)	-	-	-	-

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Other relationships					
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Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis)					
		D. Simon	Bieber	Wollenberg	Schwennesen
1	Grant	-	-	Astellas, Novartis	-
2	Consulting fee or honorarium	-	Astellas Novartis Sanofi LEO Pierre Fabre	Astellas, Basilea, Bayer, GSK, Hickma, Karrer, L'Oreal, MEDA, MSD, Novartis, Therakos,	-
3	Support for travel to meetings for the study or other purposes	-	Astellas	Astellas, Basilea, Biocon	-
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	-	-	-	-
5	Payment for writing or reviewing the manuscript	-	-	-	-
6	Provision of writing assistance, medicines, equipment, or administrative support	-	-	-	-
7	Other	-	-	-	-

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Relevant financial activities outside the submitted work					
1	Board membership	none	-	-	-
2	Consultancy	Astellas (Schweiz) AG	-	Merck	-
3	Employment	none	-	-	-
4	Expert testimony	Basilea Pharmaceutical	-	Merck	-
5	Grants/grants pending	OPO Foundation	-	Merck	-
6	Payment for lectures including service on speakers bureaus	-	-	Amgen, Merck, Roche	-
7	Payment for manuscript preparation	-	-	Roche	-
8	Patents (planned, pending or issued)	-	-	-	-
9	Royalties	-	-	-	-
10	Payment for development of educational presentations	-	-	-	-
11	Stock/stock options	-	-	-	-
12	Travel/accommodations/meeting	Janssen (EADV 2011)	-	-	-

	expenses unrelated to activities listed**				
13	Other (err on the side of full disclosure)	-	-	-	-

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Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	-	-	-	-

Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis)					
		Szepietowski	Werfel	Stingl	Ring
1	Grant	-	-	-	-
2	Consulting fee or honorarium	-	-	-	-
3	Support for travel to meetings for the study or other purposes	-	-	-	-
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	-	-	-	-
5	Payment for writing or reviewing the manuscript	-	-	-	-
6	Provision of writing assistance, medicines, equipment, or administrative support	-	-	-	-
7	Other	-	-	-	-

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Relevant financial activities outside the submitted work					
1	Board membership	-	-	-	-
2	Consultancy	-	-	-	-
3	Employment	-	-	-	-
4	Expert testimony	-	-	-	-
5	Grants/grants pending	-	-	-	-
6	Payment for lectures including service on speakers bureaus	-	-	-	-
7	Payment for manuscript preparation	-	-	-	-
8	Patents (planned, pending or issued)	-	-	-	-
9	Royalties	-	-	-	-
10	Payment for development of educational presentations	-	-	-	-
11	Stock/stock options	-	-	-	-
12	Travel/accommodations/meeting expenses unrelated to activities listed**	-	-	-	-
13	Other (err on the side of full disclosure)	-	-	-	-

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Conflicts of interests

Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis)				
		Lipozencic	Luger	Schäfer
1	Grant	-	-	-
2	Consulting fee or honorarium	-	-	-
3	Support for travel to meetings for the study or other purposes	-	-	-
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	-	-	-
5	Payment for writing or reviewing the manuscript	-	-	-
6	Provision of writing assistance, medicines, equipment, or administrative support	-	-	-
7	Other	-	-	-

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Relevant financial activities outside the submitted work				
1	Board membership	-	-	-
2	Consultancy	-	-	-
3	Employment	-	-	-
4	Expert testimony	-	-	-
5	Grants/grants pending	-	-	-
6	Payment for lectures including service on speakers bureaus	-	-	-
7	Payment for manuscript preparation	-	-	-
8	Patents (planned, pending or issued)	-	-	-
9	Royalties	-	-	-
10	Payment for development of educational presentations	-	-	-
11	Stock/stock options	-	-	-
12	Travel/accommodations/meeting expenses unrelated to activities listed**	-	-	-
13	Other (err on the side of full disclosure)	-	-	-

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Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	-	-		-

Conflicts of interests

**ORANJE
ARNOLD**

The Work Under Consideration for Publication				
1	Grant			
2	Consulting fee or honorarium	/		
3	Support for travel to meetings for the study or other purposes	/		
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	/		
5	Payment for writing or reviewing the manuscript	/		
6	Provision of writing assistance, medicines, equipment, or administrative support	/		
7	Other			

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work				
1	Board membership			
2	Consultancy			
3	Employment			
4	Expert testimony			
5	Grants/grants pending	SCHERING PLAUGH	manlycke	
6	Payment for lectures including service on speakers bureaus	/		
7	Payment for manuscript preparation	/		
8	Patents (planned, pending or issued)	/		
9	Royalties			
10	Payment for development of educational presentations	/		
11	Stock/stock options			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	/		
13	Other (err on the side of full disclosure)	/		

* This means money that your institution received for your efforts.

** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	NARROW COOPERATION WITH GLAXO SMITH KLINE concerning Fluticasone propionate and TIS (three-items - severity score)			

Alomar, Agustín - has been speaker for Almirall, Astellas, Leti
Gelmetti, Carlo - no conflicts of interests declared

Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis)

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For the European Dermatology Forum (EDF), and the European Academy of Dermato-Venereology (EADV), and European Federation of Allergy (EFA), and the European Society of Pediatric Dermatology (ESPD)

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Summary

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

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

Introduction

Atopic eczema (AE) (= atopic dermatitis, eczema, “Neurodermitis” in German speaking countries, endogenous eczema) is an inflammatory, pruritic, chronic or chronically relapsing skin disease occurring often in families with other atopic diseases (bronchial asthma and/ or allergic rhinoconjunctivitis) (Johansson et al. 2001).

AE is one of the most common skin diseases which effects up to 20 % of children and 1-3 % of adults in most countries of the world (Williams 2000). AE is often the first step in the development of other atopic diseases as rhinitis and/or asthma.

In the diagnoses of AE several criteria have been established (Hanifin and Rajka 1980, Williams et al. 1994). There is no pathognomonic laboratory biomarker for diagnosis of AE, since the most typical feature, the elevation of total or allergen-specific IgE levels in serum or the detection of IgE-mediated sensitization in the skin test, is not present in all individuals suffering from AE; for this latter group the term “intrinsic” (non-IgE-associated) AE has been introduced to distinguish it from “extrinsic” (IgE-associated) forms of AE (Wüthrich 2003). This controversy in terminology is going on until today (Johansson et al. 2001; Johansson et al. 2004) and has practical implications with regard to specific avoidance strategies in the management of this disease.

In the etiopathophysiology of AE several aspects have to be taken into consideration:

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

- Immune deviation towards Th2 in the initiation phase with consequent increased IgE production
- Deficient skin barrier function (“dry” skin) due to abnormal lipid metabolism and/ or epidermal structural protein formation (filaggrin mutation, protease inhibitor deficiency, etc.)
- Abnormal microbial colonization with pathogenic organisms such as *Staphylococcus aureus* or *Malassezia furfur* (compared to *Staphylococcus epidermidis* in normal individuals) and subsequent increased susceptibility to skin infection
- Strong psychosomatic influence with an imbalance in the autonomic nervous system with subsequent increased production of mediators from various inflammatory cells (e.g. eosinophilic leukocytes).

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

After establishing the diagnosis of AE, the severity of the disease has to be determined. The classical method is the “Scoring of Atopic Dermatitis” (SCORAD) developed by the European Task Force of Atopic Dermatitis (ETFAD). The SCORAD has been modified by several authors (Kunz et al. 1997). AE with a SCORAD higher than 40 is generally regarded as “severe”, while AE with a SCORAD below 20 can be regarded as “mild”.

It has to be mentioned that the majority of cases with AE can be regarded as “mild” with 10 to 20 % of patients suffering from severe eczematous skin lesions (Kunz et al. 1997); this percentage seems to be higher in the adult AE population.

In the following the most important strategies in management and medication will be briefly discussed.

Methods

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

Base of the guideline

The existing evidence-based National guideline from Germany (Werfel et al. 2009), the HTA report (Hoare 2000) as well as the position statement of the ETFAD (Darsow et al. 2010) were compared and evaluated using the national standard Appraisal of Guidelines Research and Evaluation (AGREE). The committee decided that all the documents fulfilled enough criteria to be used as the base of the new evidence-based European Guidelines on Treatment of Atopic Eczema.

Data base and literature search

Newer literature published after the German Guidelines (Werfel et al. 2009) and the ETFAD Position Statement (Darsow et al. 2010) was searched using medline, EMBASE and the Cochrane Library.

Evaluation of the literature

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

Table 1 Grades of evidence

- 1a) Metaanalysis 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

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

Table 2 Classification of strength of recommendation

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

Consensus process

The committee designated especially important areas as those requiring consensus. The consensus process consisted of a nominal group process and a DELPHI procedure.

Consensus conferences were held in Berlin October 2009, Cavtat May 2010, Munich July 2010 and Goteborg October 2010, where the sections regarding consensus were discussed by the entire guidelines group following a formal consensus process.

External review

According to the EDF standard operation procedure all European dermatological societies were invited to review the guidelines prior to the last internal review. The comments of the participating societies were forwarded to the chapter authors and considered during the last internal review.

Update of the guidelines

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

Target group

This guideline has been prepared for physicians, especially dermatologists, pediatricians, general practitioners and all specialists taking care of patients suffering from AE.

Also patients and relatives should be able to get reliable information and evaluation with regard to evidence-based therapeutic modalities.

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

Emollient therapy and skin care

Dry skin is one of the main symptoms of AE and part of the definition. There is now scientific evidence in humans and mice of genetically driven skin barrier anomalies that facilitate allergen penetration into the skin with an increased proneness to irritation and subsequent cutaneous inflammation. Filaggrin deficiency is the best defined anomaly, which gives rise to a deficiency in small water binding molecules resulting from normal filaggrin catabolism (Palmer et al. 2006). 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 (Briot et al. 2009).

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. 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.

Adding Sodium hypochlorite to the bath-water seems very important because of its bacterial count inhibiting activities. It may be advised to every treatment in AE. A recently published study by Huang et al. (2009) showed that children who took a bath using half a cup of bleach per full standard tub were relieved of their AE related itching. The bleach apparently had very little odor. Salt baths may be beneficial because of removing the dead keratolytic material (Ludwig 1968). In heavily impetiginized or ichthyotic skin salt baths are useful.

Emollient therapy

The direct use of emollients on inflamed skin is poorly tolerated and it is better to treat the acute flare first. Emollients are the mainstay of maintenance therapy. Hydration of the skin is usually maintained by at least twice daily application of moisturizers with a hydrophilic base, e.g. 5% urea. The use of barrier ointments, bath oil, shower gel, emulsions or micellar solutions enhancing the barrier effect is also recommended. The cost of high quality (low in contact allergens) emollient therapies often restrict their use because such therapies are considered to be non-prescription drugs (except for e.g. Finland where prescription and reimbursement are usual) and

the quantities required are usually high (150–200 g per week in young children, up to 500 g in adults).

A better molecular and biochemical knowledge of the skin in AE should provide access to barrier improving topical agents. There is limited evidence-based proof for the use of emollients (Breternitz et al. 2008).

Ingredients and possible risks of emollients

Glycerol seems better tolerated (less smarting effect) than urea plus sodium chloride (Loden et al. 2002). Usually, the recommendation is to use emollients immediately after bathing and soft pad drying. A small study suggests that emollient applied alone without bathing have a longer duration as measured by capacitance (Chiang & Eichenfield, 2009).

Propylene glycol is easily irritating in young children aged less than two years and should not be used in these young children. There is evidence that the large preventive use of emollients containing allergens such as peanut (Lack et al. 2003) or oat (Boussault et al. 2007) may increase the risk of skin sensitization and allergy. Only emollient preparations devoid of proteinaceous allergens and haptens (contact allergy) should be used, especially in the most vulnerable age group before the age of two years.

Sole use of emollients without sufficient topical anti-inflammatory therapy involves a considerable risk for disseminated bacterial and viral infection, which is already increased in AE patients (Wollenberg et al. 2003).

Evidence of efficacy:

Certain moisturizers could improve skin barrier function in atopics and reduce skin susceptibility to irritants. Loden et al. (1999) found in a comparative study between a glycerol-containing cream and placebo an improvement over time in both groups indicating the importance of emollient treatment in AE. Another study in adult AE patients suggested an effect of coconut oil on staphylococcus aureus carriage (Verallo-Rowell et al. 2008).

Evidence of steroid sparing effects

1. Short term (3-6 weeks)

Several studies in children (e.g. Grimalt et al. 2007 ; Szczepanowska et al. 2008) and one in a mixed children-adult population (Eberlein et al. 2008) 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 derived comparable results for intermittent emollient therapy and time to relapse, using comparable study designs in adults and children (Berth-Jones et al. 2003 ; Glazenburg et al. 2007).

Regimens for basic/maintenance therapy are still awaiting validation based on systemic reviews and a Cochrane review (Oranje in prep.).

Recommendations:

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

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

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

Avoidance strategies

Many patients are desperate when they hear from their physicians that AE is not "curable". It is important to explain the difference between the genetic predisposition towards hypersensitive and dry skin which cannot be "cured" today and the acute eczematous skin lesions which can very well be treated and disappear. The identification of individual provocation factors is crucial in the management of AE and their avoidance allows longer phases of remission or total clearance of symptoms.

In avoidance recommendations one has to distinguish between primary, secondary and tertiary prevention measures.

Among provocation factors, specific and non-specific elicitors have to be distinguished.

Non-specific provocation factors

Numerous factors and substances from the environment can irritate the sensitive skin of patients with AE and can elicit eczema flares. They may be physical, like mechanic irritants (e.g. wool), chemical (acids, bleaches, solvents, water) or biological (microbes) in nature. Information on unspecific irritants and their role in aggravating eczema is a crucial prerequisite for long-term management of patients with AE. Here also the adequate skin care and hygiene procedures in cleansing and dressing have to be discussed with the patient (see also, "Educational program, eczema school").

Negative effects of air pollutants upon the development and maintenance of AE, like tobacco smoke or volatile organic compounds (VOCs) in indoor environments and traffic exhaust in the outdoor air have to be mentioned. There is evidence from epidemiological trials that exposure to indoor chemicals, such as formaldehyde, increases skin barrier disturbance (Eberlein et al. 1998); 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 (Huss-Marp et al. 2007).

Exposure to traffic exhaust has been shown to be associated with an increased risk to develop AE in pre-school children (Krämer et al. 1999, Morgenstern et al. 2008).

Exposure to environmental tobacco smoke measured as urinary cotinin / creatinin ratio was associated with a significant elevated risk to develop atopic eczema which was especially pronounced in children of parents with an atopic background (Krämer et al. 2004).

Avoidance strategies regarding tobacco smoke as well as traffic exhaust exposure in young children have been introduced in the recent S3 Guideline for primary prevention of atopy in Germany (Schäfer et al. 2004, Muche-Borowski et al. 2010).

Certain food ingredients like alcohol, additives or vasoactive amines may also trigger eczematous skin flares (Vieluf et al. 1999) (see also "Food allergy").

Specific allergen avoidance

Aeroallergens

Aeroallergens have been shown to elicit eczematous skin lesions. In a rather high percentage of patients with AE (30-50 %) the atopy patch test (APT) is positive (30-50%) (Darsow et al. 1999). Most common airborne allergens eliciting eczema are

derived from house dust mites of the species *Dermatophagoides pteronyssinus* and *D. farinae*.

Also mold exposure in damp indoor environment has been found to be associated with increased eczema risk (Schäfer et al. 2004).

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 allergen present in the room. Encasings of mattresses and beddings protect humans from mites contained in mattresses. There are also mite-proof pyjamas ("eczema overalls"). There are some studies showing a clear-cut benefit from house dust mite avoidance strategies in the improvement of AE (Tan et al. 1996).

Rehabilitation programs in mite-free environments – like in alpine climate – have shown to lead to significant and long-lasting improvement of AE (see also "Climate therapy") (Vocks 1994, Engst 2000, Eberlein 2009).

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 (Krämer et al. 2005). Pollen avoidance is difficult under everyday conditions in most parts of Europe except when air conditioning with pollen filters is used in the indoor environment. In high altitude mountain climate pollen counts are usually lower than in the average living areas.

Animal epithelia

Many patients are already aware that contact with animals is leading to a deterioration of the skin symptoms.

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.

There is no evidence that dogs increase the risk of AE in children.

Once a patient is sensitized and allergic to a pet, avoidance is absolutely necessary.

There is no evidence that pet keeping has a preventive effect on primary prevention of AE among normal population.

Dietary Recommendations

See chapter "Food allergy"

Clothing and textiles

Smooth clothing and avoidance of irritating fabrics and fibers is essential in the avoidance of primary skin irritation. Too occlusive clothing inducing heat sensations should be avoided.

Early ear-piercing and use of nickel-releasing jewelry has been found to be associated with a significantly elevated risk of nickel contact allergy in young girls (Kunz et al. 1990).

Special recommendations have to be given in individual counseling programs with regard to the choice of profession. There is common consensus that occupations with marked skin-damaging activity or contact with strongly sensitizing substances should be avoided by patients with AE (Diepgen et al. 2000).

Recommendations

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

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

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

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

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

Dietary intervention

Food allergens

Among food allergens, cow's milk, hen's egg, wheat, soy, tree nuts and peanuts are most frequently responsible for eczema or exacerbation in infancy (Werfel 2004). In older children, adolescents and adults pollen related food allergy should be taken into account (Breuer 2004, Reekers 1999).

Different types of clinical reactions to food have been described in patients with AE: Early reactions, such as urticaria, gastrointestinal or respiratory symptoms occur within 120 minutes after the administration of the allergens. Late phase responses, manifesting as eczematous lesions, occur after 2-48 hours or some days. After oral food challenge, about 50% of children with AE who reacted to food showed both immediate and delayed reactions and 15% showed worsening of eczema only (Breuer et al. 2004). The personal history is often not helpful predicting late reactions to food with a positive predictive value of only 30% as opposed to 80% for immediate reactions.

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

Atopy patch tests (APTs) are performed with self-made food material applied to the back with large test chambers for 48-72 hours. Food APT are not standardized for routine use (Turjanmaa et al. 2006). So far, APTs have demonstrated to improve the accuracy of skin testing in the diagnosis of allergy to cow's milk, egg, cereals, and peanuts in AE patients (Isolauri et al. 1996, Majamaa et al. 1999, Darsow et al. 2000, Niggemann et al. 2001, Roehr et al. 2001, Strömberg 2002, Seidenari et al. 2003). Whereas immediate-type reactions are associated with SPT positivity, delayed ones are related to positive responses to APTs. However, food challenge is not replaced by patch testing (Mehl et al. 2006).

The **double-blind placebo-controlled food challenge** (DBPCFC) is considered the gold standard for diagnosing food allergy (Bindselev-Jensen 2001). In AE the evaluation of delayed reactions after 24h or 48 hours by trained personal is mandatory as stated by a recent position paper of the EAACI (Werfel et al. 2007). Challenge tests based on repeated exposure to food enable the assessment of delayed adverse responses. (Isolauri et al. 1996, Majamaa et al. 1999, Strömberg 2002, Seidenari et al. 2003). The major flaw is that they do not offer the opportunity to exclude placebo reactions and/or coincidental influences of other trigger factors of AE during the prolonged challenge period.

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

In systematic review (Hoare et al. 2000) eight randomised, controlled studies concerning the effect of an elimination diet on existing atopic eczema were identified and summarized in the following way:

- Elimination diets are difficult to be performed even in a motivating atmosphere during a clinical study.
- The drop-out-rate in atopic eczema studies is particularly high in studies on diets.
- There is no convincing evidence that a milk- or egg-free elimination diet is beneficial in general when unselected groups of patients with atopic eczema were studied.
- There is no evidence for a benefit in the use of elementary or few food restricted diets in patients with atopic eczema.

A recently published systematic review identified a single prospective controlled study that supports the notion that a direct elimination diet (in the study: egg exclusion) may be beneficial for the course of AE in sensitized patients with clinical symptoms upon ingestion of eggs (Bath-Hextal et al. 2009).

Recommendations:

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

Topical anti-inflammatory therapy

Topical treatment

Effective topical therapy depends on three fundamental principles: sufficient strength, sufficient dosage and correct application. Topical treatment should always be applied on hydrated skin, especially when using ointments. The emollient should be applied first when it is a cream, 15 min before the anti-inflammatory topical is applied and when it is an ointment 15 min after. Patients with acute, oozing and erosive lesions, and children in particular, sometimes do not tolerate standard topical application, and may first be treated with 'wet wraps' until the oozing stops. They are highly effective in acute eczema and improve tolerance. The use of wet-wrap dressings with diluted corticosteroids for up to 14 days (usual is rather up to 3 days) is a safe crisis intervention treatment of severe and/or refractory AE with temporary systemic bioactivity of the corticosteroids as the only reported serious side-effects. (Devillers & Oranje 2006, Schnopp et al. 2002) Even without wet wraps, topical therapy is time consuming: patients should plan 30 min for one session. One well-conducted treatment per day is usually sufficient; oozing eczema may require a few days with higher treatment frequency.

By tradition, anti-inflammatory topical therapy has been administered to lesional skin only and has been stopped or tapered down once visible lesions were cleared. This traditional, reactive approach has in the last years been challenged by the proactive treatment concept, which is defined as a combination of predefined, long-term, low dose, anti-inflammatory treatment applied to previously affected areas of skin in combination with liberal use of emollients on the entire body and a predefined appointment schedule for clinical control examinations (Wollenberg et al. 2009). The first trial with intermittent topical steroid use was published already in 1999 (Van der Meer et al. 1999). The proactive, usually twice weekly treatment regimen is started after all lesions have successfully been treated by an intensive, usually twice daily treatment approach in addition to ongoing emollient therapy for previously unaffected skin. Clinical trial data are available for a number of steroid products as well as for tacrolimus ointment (Van der Meer 1999, Wollenberg & Bieber 2009).

Application amount of topical anti-inflammatory therapy should follow the finger-tip unit rule. A finger-tip 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.

Glucocorticosteroids

Topical glucocorticosteroids are a first-line anti-inflammatory treatment, applied on inflammatory skin according to the needs (pruritus, sleeplessness, new flare). Numerous substances are available in a variety of formulations. Evidence-based anti-inflammatory effects in AE were reported by different investigators (Van der Meer et al. 1999, Hanifin et al. 2002, Berth-Jones et al. 2003). With mild disease activity, a small amount of topical corticosteroids twice to thrice weekly (monthly amounts in the mean range of 15 g in infants, 30 g in children and up to 60–90 g in adolescents and adults), associated with a liberal use of emollients generally allows a good maintenance keeping SCORAD values below 15–20. Such monthly amounts of even potent topical steroids usually do not have adverse systemic or local effects.

Topical corticosteroids are grouped by potency, which should be known to prescribers. In addition, there are different generations of substances, which may differ in their risk-benefit ratio. Potent and very potent corticosteroids (group III and IV) are more likely to cause depression of adrenal function than group I (mild) and II (moderate strength) treatments, but their systemic effects will decrease more quickly due to more rapid restitution of the skin barrier (Walsh et al. 1993). Itch is the key symptom for evaluation of response to treatment, and tapering should not be initiated before the itch has disappeared. Dose tapering should be gradual to avoid withdrawal rebound; tapering strategies consist in using a less potent corticosteroid on a daily base, or keeping a more potent one while reducing the frequency of application (intermittent regimen). One well-conducted, correctly dosed treatment per day is sufficient (Queille et al. 1984, Charman & Williams 2003). The most constructive way to spare steroids and avoid steroid-related side-effects is not to spare them during acute flares, but through consequent baseline emollient skin care combined with early anti-inflammatory intervention to stabilize the disease and prevent treatment-intensive flares (Eichenfield et al. 2003). Usually one daily application of topical steroids is sufficient.

Twice weekly application of fluticasone significantly reduced the risk of relapses of eczema in a „proactive“ strategy (Van der Meer et al. 1999, Hanifin et al. 2002, Berth-Jones et al. 2003).

The combination of topical corticosteroids with topical calcineurin inhibitors does not seem to be useful. At least in paediatric patients with severe AE, the efficacy and safety profile of pimecrolimus cream 1% combined with fluticasone were similar to that of fluticasone alone (Meurer et al. 2010).

In a recent paper, it has been observed that glucocorticoids inhibited the double-stranded RNA (dsRNA)-induced release of thymic stromal lymphopoietin in the atopic cytokine milieu at much lower concentrations than calcineurin inhibitors, suggesting that they could be effective in the treatment of AE when exogenous or endogenous dsRNA is involved in the pathogenesis (Lee et al. 2010).

Recommendations

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

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

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

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

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

Topical calcineurin inhibitors

Both topical calcineurin inhibitors, tacrolimus ointment and pimecrolimus cream, are licensed for topical eczema treatment. Various aspects of these drugs have been reviewed in detail (Bornhövd et al. 2001, Alomar et al. 2004). The efficacy of both

formulations has been demonstrated against placebo in clinical trials for short-term (Ruzicka et al. 1997, Van Leent et al. 1998) and long-term use of these substances (Reitamo et al. 2000, Meurer et al. 2002). In addition, proactive tacrolimus ointment therapy has been shown to be safe and effective for up to 1 year in reducing the number of flares and improving the quality of life in adult patients and children (Wollenberg 2008, Thaci et al. 2008). The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a corticosteroid with intermediate activity (Reitamo et al. 2002) while the latter is clearly more active than 1.0% pimecrolimus cream (Chen et al. 2010).

Safety data of both topical calcineurin inhibitors have been reported in many clinical trials, demonstrating the safety of these drugs in daily routine use. The most frequently observed side-effect is a transient warmth sensation or transient burning at the application site during the first days of application.(Ruzicka et al. 1997, Chen et al. 2010). It starts about 5 min after each application of the drug and may last up to 1 h, but intensity and duration typically decrease within 1 week to zero (Bornhövd et al. 2002). Generalized viral infections such as eczema herpeticum (EH) or eczema molluscum (EM) have been observed during topical calcineurin inhibitor treatment (Lübbe 2000, Wetzel & Wollenberg 2004), but a high number of clinical trials failed to demonstrate an increased frequency (reviewed in Wahn et al. 2002, Lübbe et al. 2003, Bornhövd & Wollenberg 2003). In contrast to corticosteroids, none of the topical calcineurin inhibitors induces skin atrophy (Reitamo et al. 1998, Queille-Roussel et al. 2001). 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 the induction of lymphoma over a period of 6 years (Arellano et al.2007) or photocarcinogenicity for topical calcineurin inhibitors (Margolis et al.2007, Ring et al. 2005), but since the continuous oral administration of the calcineurin inhibitor cyclosporine is associated with an increased photocarcinogenicity risk in solid organ transplant patients, UV protection e.g. with sunscreens has been advised (Reitamo et al. 2002 JACI). The use of topical calcineurin inhibitors under wet wraps or on erosive lesions may increase systemic absorption.

The efficacy of long-term monotherapy with tacrolimus ointment has been shown in children and adults (Reitamo et al. 2002, Reitamo et al. 2002 JACI). Less data are available for children under 2 years of age (Patel et al. 2003). Pimecrolimus cream has been studied in infants and children in a combination regimen with topical corticosteroids (Ho et al. 2003, Eichenfield et al. 2002), 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 from a 4-year tacrolimus and 26 weeks pimecrolimus study (Reitamo et al. 2008, Langley et al. 2008).The cost effectiveness of proactive therapy with topical tacrolimus has been demonstrated for moderate AE and is even higher in severe AE in a recent study with adult patients (Wollenberg et al. 2008), whereas the cost effectiveness of first-line treatment with topical calcineurin inhibitors has not been shown conclusively. However, in children with AE, twice-weekly treatment with tacrolimus 0.03% ointment has been observed to reduce the number of flares and to prolong time spent free from flares with no additional cost in children with moderate AE, and may be cost-saving in those with severe AE (Thaci et al. 2010).

In addition, the long-term, effective treatment of patients with AE may have a beneficial effect also on respiratory symptoms, and serum IgE (Mandelin et al. 2010

JDT). In adults, long-term treatment with 0.1% tacrolimus ointment appears to be at least as effective as a corticosteroid regimen for the trunk and extremities, and more effective in the face and neck area. Both topical tacrolimus and corticosteroids increase skin recall activity, and decrease serum IgE in patients with good treatment response. Taken together, these results suggest that skin inflammation in AE should be treated effectively, which could lead to an improvement in the Th1/Th2 balance in the skin, and to long-term improvement in the severity of the AE (Mandelin et al. 2010 Acta).

These drugs are recommended for use as second-line therapy for the short-term and noncontinuous treatment of AE in patients who do not respond adequately to topical corticosteroids or in whom they are contraindicated. According to the latest knowledge, there is no scientific evidence of an increased risk for malignancy due to a topical treatment with calcineurin inhibitors (Thaci & Salgo 2010).

Recommendations

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

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

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

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

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

Anti-pruritic therapy

Itch is the most important clinical symptom in AE, with peculiar impact on emotional dimensions of perception as compared to other pruritic dermatoses like urticaria (Darsow et al. 2001). Concerning pruritus accompanying AE, only few studies investigate the antipruritic effect only. In most studies, pruritus is part of the total symptom score using the EASI and SCORAD. For example, topical and systemic corticosteroids, topical calcineurin inhibitors, cyclosporine and UV-irradiation have significant influence on pruritus while only single studies specifically investigate the relief of pruritus intensity (table 3).

Antipruritic therapy in AE is multidimensional treating the symptom itself, the contributing factors such as dry skin, inflammation and the related scratch lesions. Therefore, several general measures can be recommended (see “Basic Therapy”). Based on expert opinion, short term relief of pruritus can be achieved by topicals containing urea, camphor, or menthol preparations as well as wet, cooling or fat-moist-wrappings (Lee et al. 2007), wrappings with black tea, short and lukewarm showers. Unspecific physical modalities are described to be beneficial like acupuncture (Pfab et al. 2010), and cutaneous field stimulation (Bjorna and Kaada 1987).

Antiinflammatory therapies acting on pruritus

Glucocorticosteroids

Several studies describe the anti-inflammatory effect of topical corticosteroids in AE, in which pruritus was one parameter among others such as erythema, induration, scaling, excoriation (see chapter topical anti-inflammatory therapy). In sum, these studies suggest that topical corticosteroids have a rapid antipruritic effect and can also be used in “proactive” therapy (Peserico et al. 2008). No study focuses solely on the onset, mechanisms and duration of the pruritus relief in AE. However, it seems likely that the anti-inflammatory effect of glucocorticosteroids is responsible to partly abolish pruritus (Kawashima et al. 2003). This also holds true for systemic glucocorticosteroids, for which no specific studies on an anti-itch effect in AE were published.

Recommendations

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

Interferon (INF) gamma

Interferon gamma appears to have a beneficial effect on pruritus in AE (Reinhold et al. 1993). In a double-blind study, pruritus was reduced by 50% even 1-2 years after long-term treatment with recombinant human interferon gamma (Stevens et al. 1998).

Recommendations

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

Calcineurin inhibitors

Topical calcineurin inhibitors relieve significantly pruritus in AE. Itch is completely relieved after the first days of treatment in adults and children. Studies report of relief even 3 days of topical application of tacrolimus (Boguniewicz et al. 1998, Nakagawa et al. 1994) and pimecrolimus (Luger 2001 et al., Eichenfield et al. 2007).

Recommendations

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

UV-therapy

UV irradiation reliefs pruritus in AE what was demonstrated in a study that compared UVB to placebo treatment (Jekler & Larko 1988). Also a study proved that Narrowband-UVB was more effective than Broadband-UVA (Reynolds et al. 2001) and UVA1 (Legat et al. 2003).

Recommendations

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

Cyclosporine A

See "Systemic Immunosuppression"

Intravenous Immunoglobulin therapy

See "Systemic Immunosuppression"

Mycophenolat mofetil

See "Systemic Immunosuppression"

Specific antipruritic therapies

Topical anaesthetics

Local anaesthetics such as benzocaine, lidocaine, polidocanol as well as a mixture of prilocaine and lidocaine are widely used as short-term effective topical antipruritics. In experimental studies, the antipruritic effect of local anaesthetics was demonstrated in AE (Weisshaar et al. 1997) but controlled clinical trials investigating the antipruritic effects of local anaesthetics in AE are pending. Case series described the efficacy of a combination of polidocanol and 5% urea (Schommer et al. 2007). In children with AE, the combination showed a pruritus improvement of 30% in comparison with an emollient (Hauss et al. 1993). None of these substances is licensed for AE in Europe.

Recommendations

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

Cannabinoid receptor agonist

Topical cannabinoid receptor agonists have been described to exhibit antipruritic and analgesic properties. Experimentally induced pain, itch and erythema could be reduced by application of a topical cannabinoid agonist (Dvorak et al. 2003). One cosmetic product containing the cannabinoid agonist N-palmitoylethanolamin was used in a multicentric, large cohort, open label study as adjuvant treatment in AE (Eberlein et al. 2008). 2456 patients including over 900 children applied the cream twice daily. Pruritus and the need to use corticosteroids were reduced up to 60%.

Recommendations

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

Capsaicin

Capsaicin, a naturally occurring alkaloid and the principal pungent of hot chilli peppers, has been advocated to be antipruritic in various dermatoses. Repeated topical application of capsaicin releases and prevents specifically the reaccumulation of neuropeptides in unmyelinated, polymodal C-type cutaneous nerves. Capsaicin exerts its functions via binding to a capsaicin-specific receptor, i.e. the transient receptor potential channel vanilloid (TRPV1) which is located on free nerve endings. Concerning AE, experimental studies (Weisshaar et al. 1998) and case series (Reimann et al. 2000) report on clear itch reduction. No controlled study was performed as of yet.

Recommendations

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

Topical doxepin

5% doxepin cream exhibited antipruritic effects in controlled studies in AE (Drake et al. 1994). 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.

Recommendations

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

Topical mast cell stabilizers

Mast cell mediators such as tryptase and histamine contribute to induction of pruritus in AE. Accordingly, the application of mast cell degranulation inhibitors or stabilizers seems reasonable. However, in a multicenter, double-blind, placebo-controlled trial applying 3% hydrogel formulation of tiacrilast (mast cell inhibitor) against vehicle in atopic dermatitis, there was no significant improvement of pruritus (Czarnetzki et al. 1993). In another study, pruritus in children with AE responded to topical sodium cromoglycate (Haider 1977), which was proven by a recent placebo-controlled study (Stainer et al. 2005).

Recommendations

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

Leukotriene receptor antagonists

Preliminary studies showed reduction of pruritus in patients with AE during treatment with the leukotriene receptor antagonists zafirlukast and zileuton (Carruci et al. 1998, Zabawski et al. 1999, Woodmanse et al. 1999). However, due to a high rate of side-effects the substances were not developed to regular therapies of AE.

Recommendations

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

Opioid receptor antagonists naltrexone and nalmefene

The mu-opioid receptor antagonist nalmefene was applied in controlled, randomized studies in AE. A dosage of 10 mg and 20 mg each once per day showed significant relief of pruritus in three studies (Monroe 1989, Burch et al. 1988, Banerji et al. 1988). In open label trials and one double-blind, placebo-controlled study trial, the only orally active mu-opioid antagonist naltrexone 25 - 150 mg per day showed considerable

antipruritic effects (Metze et al. 1999; Malekzad et al. JEADV 2009). None of these substances is currently licensed for treatment of AE itch.

Recommendations

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

Selective serotonin reuptake inhibitors

The antipruritic effect of the selective serotonin reuptake inhibitor paroxetine and fluvoxamine was investigated in an open label trial in dermatological patients. Single patients with pruritus due to AE were included which responded with considerable reduction of pruritus. In these patients, the pruritus was reduced about half of intensity (maximal antipruritic effect score, 45.0 +/- 7.1%) (Ständer et al. 2009).

Recommendations

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

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

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

*as proven by randomised, controlled trials

T, topically; o, orally

Antihistamines

Antihistamines have been used for decades, in an attempt to relieve pruritus in patients with AE. However, only a few randomized controlled trials have been conducted and they have in the majority shown only a weak or no effect in decreasing pruritus (Doherty et al. 1989, Henz et al. 1998, Langeland et al. 1994, La Rosa et al. 1994, Wahlgren et al. 1990, Munday et al. 2002).

The first generation of sedative antihistamines such as hydroxyzine, clemastine fumarate and dimetinden maleate may allow a better sleep pattern in acute situations with exacerbations of eczema (evidence level D). Concerning the newer non-sedating antihistamines, single studies using loratadine, ceterizine or fexofenadine demonstrated no or only a weak relief of pruritus in AE (Chunharas et al. 2002, Hannuksela et al. 1993, Kawakami et al. 2006) (table 4). A significant, but clinically small, antipruritic effect of fexofenadine 60 mg twice daily has been described (Kawashima et al. 2003). An effect on itch of a high dosage of 20 to 40 mg ceterizine daily has been observed, but this effect was primarily attributed to sedation (Hannuksela et al. 1993).

Diepgen et al. reported in infants with severe AE a corticosteroid sparing effect of ceterizine and judged this as an indirect measure for the efficacy of ceterizine on pruritus (Diepgen et al. 2002). Murata et al. (2010) compared in patients with pruritic diseases (including eczema cases) effects of sedating and nonsedating antihistamines: similar effects on itch intensity were seen, but only nonsedating antihistamines reduced significantly the impairment in work productivity and daily activity.

In general, antihistamines are safe to use, also for a long period of time (Simons 2007), and the major advantage seems to be relief of the symptoms of co-morbidities such as allergic asthma, rhino-conjunctivitis, urticarial dermatographism and urticaria. Topical antihistamines have no effect on itch beyond that of their cooling vehicles.

Summary of evidence-based data:

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

Recommendations

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

Antimicrobial therapy

A number of defects in innate cutaneous immunology may explain the high rate of cutaneous colonization with *Staphylococcus aureus* (up to 90% in moderate to severe eczema) in AE (de Benedetto et al. 2009, Niebuhr et al. 2010). There is evidence for an association of *S. aureus*-derived exotoxins including superantigens and pore forming hemolysins with disease exacerbation (Bunikowski et al. 2000, Zollner et al. 2000, Wichmann et al. 2009, reviewed by de Benedetto 2009 and Niebuhr 2010), supporting early observations that the density of *S. aureus* colonization in AE is significantly correlated with clinical severity (Hauser et al. 1985), and that patients with severe AE may improve (but not be cured) by anti-staphylococcal treatment (Breuer et al. 2002). In severe exacerbations systemic antibiotic treatment may be helpful.

In general, improving eczema with anti-inflammatory regimen (i.e. TCS, TCI, UV) decreases staphylococcal colonization. This led to the clinical concept that patients with high numbers of colonizing *S. aureus* can benefit from combination treatment with corticosteroids and antimicrobial treatment, in most cases using topical antiseptics like triclosan, chlorhexidine or cristal violet 0.3 % (Leyden et al. 1977, Brockow et al. 1999). In addition, a combination of natriumhypochlorite in baths with antibiotics has recently been published to have minor to moderate effects on eczema in children with AE (Huang et al. 2008). However, formal evidence on beneficial effects of topical antiseptics coming from prospective controlled studies is still not available. A recent Cochrane review did not find any benefit for antibacterial soaps (1 trial, 50 participants), or antibacterial bath additives (2 trials, 41 participants), or topical antibiotics/antiseptics (4 studies, 95 participants). (Birnie et al. 2008).

Apart from specific indications such as overt secondary infection or presence of beta-hemolytic streptococci (David and Cambridge 1986, Adachi et al. 1998) or from visual superinfections of the skin with *Staphylococcus aureus*, treatment of eczema with antibiotics had no effect in regards to clinical improvement and sparing of steroids (Ewing et al. 1998) and should therefore not be performed. Besides being not effective on the severity of eczema, antibiotic eradication of *S. aureus* as a long-term strategy bears the risk of increasing prevalence of antibiotic resistance (Shah et al. 2003, Niebuhr et al. 2008). Particularly, topical antibiotics should not be used for longer periods in the treatment of AE.

The use of silver-coated textiles and silk fabric with the durable antimicrobial finish AEGIS ADM 5772/S can reduce *S. aureus* colonization and eczema severity (Gauger et al. 2003, 2006, Ricci 2004). These newer options are still under investigation. Of note, there is some concern about the safety of silver-coated textiles in infants and toddlers.

Secondary infections with yeasts, dermatophytes, or streptococcal infections have also been implicated as trigger factors in AE (Lübbe et al. 2003). Intense erythema in skin folds of children with a flare of AE may warrant a search for streptococcal skin infection. In general, signs of secondary infections should be treated if present. Antimycotics are proposed for the treatment of “head and neck” variant of AE, often associated with *Malassezia sympodialis* superinfection (recently reviewed by Darabi 2009). Systemic ketoconazole (Lintu et al. 2001) and topical ciclopiroxolamine (Mayser et al. 2006) have been shown to improve eczema significantly within 4 weeks in placebo-controlled trials in patients with “head-neck-shoulder dermatitis”. Instead of

ketoconazol, other imidazole derivates (fluconazol or itraconazol) are proposed nowadays due to a better benefit:side effect ratio.

Viral infections are occurring more frequently in AE patients than in normal individuals, with a tendency to disseminated, widespread disease and named after the causative virus as eczema molluscatum, eczema vaccinatum or eczema herpeticum (EH) (Wollenberg, Wetzel 2003). EH has been described following corticosteroid and calcineurin inhibitor therapy, but recent data indicate that patients with severe, untreated AE, a high total serum-IgE and early onset of AE are at risk for EH, whereas pre-treatment with topical corticosteroids does not imply a risk (Wollenberg, Zoch 2003). The mainstay of EH therapy is prompt systemic antiviral chemotherapy with i.v. aciclovir, but a number of alternative treatment modalities exist (Wollenberg, Zoch, 2003).

Recommendations

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

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

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

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

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

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

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

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

Phototherapy

As most patients affected by AE improve during the sunny summer season, artificial UV radiation is frequently employed in the treatment of AE.

A recent study has confirmed that 74.4% of the patients affected by mild-moderate AE had complete resolution during summer holidays, 16.3% had improvement and only 9.3% had no modification of AE severity, confirming the seasonability of the disease, with improvement during summertime and worsening in the other seasons: More, seaside holidays produced a significantly greater improvement than mountains holidays, with complete resolution of the disease in 91.2% versus 11.1% of patients ($P < 0.01$) (Patrizi et al. 2009). 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.

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 (Legat and Wolf 2009). The known mechanism of action targets immunomodulation through apoptosis of inflammatory cells, inhibition of Langerhans cells and alteration of cytokine production (Gambichler et al. 2008). In addition, UV has an antimicrobial effect reducing the colonization of *S. aureus*, (Dotterud et al. 2008) due to its anti-inflammatory effect and improves skin barrier (Hong et al. 2008). 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 (Vähävihi et al. 2008).

Present UV sources include equipments able to emit selective spectres of radiations:

- Broadband UV (UVA + UVB = 290–400 nm)
- Broadband ultraviolet B (BB-UVB = 280-315 nm)
- Narrow-band UVB (nbUVB = peak: 311–313 nm)
- UVA1 (340–400 nm).

Treatment with longer wavelengths has not been sufficiently studied for AE and should therefore not be applied. 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 in children younger than 12 years should not be applied.

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 their dermatosis during sun exposure. In practice, the choice of a certain UV treatment is limited by the availability of the phototherapy equipments: e.g. UVA1 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.

In short, taking into account the individual tolerability, narrow-band UVB has been indicated for chronic moderate forms of AE (Williams et al. 2008) and is currently preferred to broadband UV because it is less erythemogenic, while high dose UVA1 has been prescribed for more severe phases (Gambichler et al. 2009 BJD). Medium dose UVA1 appears to be similar in terms of efficacy as narrow-band UVB (Majoie et al. 2009). Furthermore, as highlighted in a recent study, there is a small but significant proportion of psoriasis and AE patients who do not tolerate narrow-band-UVB but demonstrate an excellent clinical response to broad-band-UVB (Pugashetti et al. 2009).

Topical steroids and emollients should be considered at the beginning of phototherapy to reduce a possible flare-up, while topical immunosuppressors as tacrolimus and pimecrolimus should be avoided. UV can also be combined with a previous (oral or topical) administration of photosensitizing drugs (psoralens): the so-called PUVA (photochemotherapy). All UV treatments and, even more, photochemotherapy, pose a long-term risk for development of skin cancer, together with the proven prematurely ageing of the skin. UV therapy has to comply with special requirements with regard to personnel, documentation, UV protection especially of the eyes, contraindications and technical aspects. Photochemotherapy is not the first choice for AE because of the proven carcinogenicity and the fact that most AE patients are young. During systemic photochemotherapy, patients must wear UVA-blocking sunglasses and also after treatment for 1 or 2 days when exposed to sunlight because psoralens are eliminated slowly. While simple UV regimens are generally well tolerated (a transient sensation of warmth should be considered normal), PUVA has a number of side-effects, which may include nausea, headache, fatigue, burning skin, itching and irregular skin pigmentation as well as an increased risk of skin cancer (Chuang et al. 1992), so the risk-benefit ratio of this treatment must be carefully weighted. However it has been demonstrated that PUVA provides a better short- and long-term response than medium-dose UVA1 in patients with severe AE (Tzaneva et al. 2010). It has been recently observed that PUVA therapy may reduce epidermal hyperinnervation of AE by normalization of axonal guidance molecules as semaphorin 3A and nerve growth factor in the epidermis (Tominaga et al. 2009).

New devices as 308 nm monochromatic excimer light expand the therapeutic options in patients with localized and therapy-resistant AE even though they can treat only limited surfaces (Mavilia et al. 2008, Wollenschläger et al. 2009). There are no prospective trials on AE patients comparing narrow-band UVB and UVA1 with more complex regimens such as heliotherapy, balneophototherapy, psoralen plus UVA (PUVA), and extracorporeal photophoresis (Gambichler et al. 2009 ADR). Pulsed-dye laser for the treatment of chronic AE is still experimental (Syed et al. 2008).

In conclusion, 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.

Recommendations

Narrow band UVB is to be preferred to broad band UVB (1a, A).

Medium dose UVA1 is similar in efficacy as narrow band UVB (1b, A).

High dose UVA1 is to be preferred in severe phases (1b, A).

Topical steroids and emollients should be considered at the beginning of phototherapy to reduce flare-up (C).

All UV treatments pose a long term risk for development of skin cancer (2a, B).

PUVA therapy is not a first choice therapy. It provides a better short and long term response than medium dose UVA1 (1b, A).

New devices as 308 nm excimer laser expand therapeutic options but have been not assessed properly in AE (-,D).

Systemic 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 no controlled trial data available that would demonstrate short term or long term (i.e. exceeding one week therapy) efficacy of continuous or intermittent therapy with systemic glucocorticosteroids against placebo or other immunosuppressive drugs. Broad experience from clinical use by many experts indicates efficacy.

Evaluation summary

Short term treatment with oral glucocorticosteroids is effective (-,D).

Recommendations

Systemic steroids have a largely unfavourable risk/benefit ratio for treatment of AE. (-,D).

Short term treatment may be an option to treat an acute flare in exceptional cases of atopic eczema. Restrictive use, largely limited to adult patients with severe atopic eczema, is recommended (-,D).

The recommended daily dose should be adjusted to body weight.

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

Ciclosporin A

Ciclosporin is licensed in many European countries for treatment of AE. Ciclosporin inhibits the production of NF-AT dependent proinflammatory cytokines in T cells.

Controlled clinical trial data demonstrating efficacy

Ciclosporin vs. Placebo - Metaanalysis

A meta-analysis of pooled data from eight RCTs (Hoare et al. 2000) clearly demonstrated the efficacy of ciclosporin in AE. Body surface area, erythema, sleep loss and glucocorticosteroid use were reduced in the ciclosporin group. The authors concluded that ciclosporine is more effective than placebo, but there is prompt relapse if ciclosporine is stopped. All Scores are back to pre-treatment values eight weeks after end of ciclosporine therapy.

Three RCTs have been published after this meta-analysis (Hoare et al. 2000):

Ciclosporin dosis finding study for AE treatment in adult patients

A fixed dosage ciclosporin regimen was evaluated in 106 adults with severe AE (Czech et al. 2000). Initial treatment was performed with 300mg/d or 150mg/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 at the 150mg/d, because this regimen showed a lower incidence of serum creatinine increase ($p < 0.1$).

Continuous or intermittent ciclosporin 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 ciclosporin regimen (Harper et al. 2000). 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.

Ciclosporin or UV Therapy for AE

Ciclosporin was tested against a combined UV/UVB regimen in a one year, open label, multicenter trial involving 72 patients (Granlund et al. 2001). Ciclosporin therapy induced a significantly higher number of days in remission, as compared to UV therapy.

Compounding of Ciclosporin

Microemulsions of ciclosporin show an earlier onset and higher peak value of efficacy compared to traditional formulations (Zurbriggen et al. 1999). The clinical efficacy evaluated after eight weeks of therapy was identical for both formulations.

Drug safety profile of ciclosporin

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

Summary of evidence-based data

Many RCTs indicate the efficacy of ciclosporin vs, placebo in AE (1a,A).

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

Side effects of cyclosporine argue against a long term treatment of AE with ciclosporin – cessation of therapy should be attempted after two years of therapy (-,D).

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

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

Ciclosporin is effective in children and adolescent atopic eczema patients (2b,B). Since an intermittent dosage regimen will lead to lower cumulative doses of ciclosporin and is effective in some AE patients, an individualized dosage regimen is recommended for underage patients (-,D).

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

Recommendations

Ciclosporin may be used in chronic, severe cases of AE in adults (1a,A).

Well known side effects of ciclosporin limit its use in AE (-,D).

An initial daily dose of 2.5-3.5 mg/kg/d and a maximal daily dose dose of 5 mg/kg/d, divided upon two single doses, are recommended. A dose reduction of 0.5-1.0mg/kg/d every two weeks is recommended, as indicated by clinical efficacy (-,D).

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

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

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

A combination therapy of ciclosporin with UV-therapy is not indicated, because the incidence of cutaneous malignancies may be increased (-,D).

Azathioprine

Azathioprine is used since many years in Great Britain and the United States 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 azathioprine was tested in a randomized, controlled, 6 month, crossover clinical trial involving 37 patients aged 17 to 73 years (Berth-Jones et al. 2002). The drop-out rate was high (12 patients on azathioprine, 4 patients on placebo). Azathioprine (2.5mg/kg bw/d) or placebo were given for three months each in a crossover design. The SASSAD skin severity score was reduced by 26% in the azathioprine group and 3% in the placebo group ($p < 0.01$). Pruritus, sleep loss and fatigue improved significantly during azathioprine, but not during placebo treatment.

Another randomized double blinded, placebo controlled, 12 weeks, clinical trial involved 63 out-patients with AE (Meggitt et al. 2006). 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 bw/d azathioprine, whereas patients with a reduced TPMT activity (heterozygous phenotype) received 1.0 mg/kg bw/d azathioprine. The azathioprine regimen was clearly 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 retrospective, uncontrolled study investigated 48 children and adolescents aged 6 to 16 years diagnosed with severe AE (Murphy et al. 2002). 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 bw/d and the dose was increased to 3mg/kg bw/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 heterogenous group of 17 children and adults from Hong Kong with a mean age of 16 years showed significant improvement of SCORAD after 3 and 6 months and significant reduction of total serum IgE levels (Hon et al. 2009).

Drug safety profile of azathioprine

The authors of the Berth-Jones study concluded, that azathioprine 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 (Berth-Jones et al. 2002). 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.

Summary of evidence-based data

Azathioprine is effective for treatment of severe atopic eczema (1b,A).

Recommendations

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

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

There are no published prospective clinical trial data regarding treatment of children and adolescents (-,D).

Mycophenolat Mofetil (MMF)

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

Controlled clinical trial data demonstrating efficacy

There is no controlled trial data available that would demonstrate the efficacy of MMF against placebo or other immunosuppressive drugs.

Some case reports or uncontrolled clinical trial data from adults indicate that it would be clinically effective in AE, Ballester et al 2009 in uncontrolled, retrospective study of 8 patients, Murray et al. 2007 in uncontrolled retrospective study of 20 patients

There is one uncontrolled retrospective report involving 14 children indicating efficacy in this age group (Heller et al. 2007: MMF 40-50 mg/kg/d in younger children and 30-40 mg/kg/d in adolescents)

Drug safety profile of MMF

Gastrointestinal adverse events, such as nausea or diarrhea, 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 thrombopenia may also occur.

Summary of evidence-based data

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

Recommendations

MMF may be used (off label) for treatment of AE in adults in a dose up to 2g/d, if ciclosporin is not effective or not indicated (4,C). There is no trial data for its use in children or adolescents (-,D).

Methotrexate (MTX)

The immunosuppressant MTX is frequently used in psoriasis, but there is only little published data on its use in AE. Some clinicians are using this drug in AE with good

success since many years. Funding of expensive clinical trials in the near future is unlikely.

Controlled clinical trial data demonstrating efficacy

An open 24 week dose escalation clinical trial involving 12 adult patients investigated the efficacy of increasing doses MTX (Weatherhead et al. 2007). The starting dose of 10mg/week was increased weekly in steps of 2.5mg/week until clinical efficacy was seen. The skin score SASSAD improved by 52% during 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 10mg/week to 25mg/week MTX showed response in 16 patients after 8-12 weeks (Lyakhovitsky et al. 2010). 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.

Drug safety profile of MTX

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-based data

An open, uncontrolled clinical trial indicates that MTX may be effective in AE (4,C).

Recommendations

MTX may be used (off label) for treatment of AE in adults, if ciclosporin is not effective or not indicated (4,C). There is no trial data for its use in children or adolescents (-,D).

Interferon gamma (IFN-g)

Some interferons may interact with the dystorted immune system of AE patients. IFN gamma (IFN-g) is a TH1 cytokine which has been shown to antagonize TH2 immune responses in vitro.

Controlled clinical trial data demonstrating efficacy

A 12 week multicentric study involving 83 patients aged 2 to 65 years compared the efficacy of subcutaneous injection of 50mg/sqm IFN-g with placebo in AE patients, who were allowed to continue topical glucocorticosteroid treatment (Hanifin et al. 1993). Significantly more IFN-g treated patients showed 50% improvement of the skin score compared to placebo. Erythema and scratch marks were significantly reduced by 30%, whereas induration, dryness, itch and lichenification were not.

A high dose (1.5 Mio IE) and a low dose (0.5 Mio IE) three times weekly IFG-g regimen were compared with placebo in 51 severe AE patients (Jang et al. 2000). Both IFG-g regimen had improved the AE after 12 weeks as compared to placebo, but there was no difference between both IFN-g treatment arms.

A randomized, prospective case control study involving 44 AE patients treated with IFN-alpha, IFN-g, Thymopentin or null therapy (Noh et al. 2001). IFN-alpha was effective in 11 of 13 treated patients, whereas IFN-g showed improvement in 2 of 10 patients. Thymopentin and null therapy were ineffective.

Drug safety profile of IFN-g

The high rate of IFN-g induced unwanted drug effects included headache (60%), muscle pain (32%) and fever (39%), all of which were significantly more frequent compared to placebo (p 0.004).

Summary of evidence-based data

IFN-g seems to be moderately effective in adult patients with severe AE (1b,A).

Some uncontrolled observations and empirical knowledge do not confirm the efficacy data from clinical trials (-,D).

The high rate of unwanted drug effects and the high treatment costs are limiting the potential use of IFN-g in chronic diseases (-,D).

Recommendations

IFN-g and IFN-alpha should not be used for treatment of AE (-,D).

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, multicentric randomized, placebo controlled clinical trial involving 1032 patients with chronic hand eczema, about one third of which are probably atopic hand eczema patients (Ruzicka et al. 2008). 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 (Grahovac et al. 2009). 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 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-based data

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,C).

Recommendations

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

Bystander improvement of extrapalmar AE lesions is likely, if alitretinoin is used to treat chronic hand eczema (4,C).

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

Biologics

Biological agents (Biologics) present a relatively new group of therapeutics created by biological processes, that include recombinant therapeutic proteins such as antibodies or fusion proteins. Biologics specifically target inflammatory cells and mediators respectively. In AE, biologics are used in order to reduce inflammation by modulating the number, activation and function of immune cells or the action of cytokines or disease relevant antibodies. A number of 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 recently. However, representative, randomized, placebo-controlled studies evaluating the efficacy and safety of biologics in AE are still not available.

T cells play a key pathogenic role in AE, therefore targeting their activation is a major approach of biologics. Alefacept, a fusion protein of lymphocyte function protein (LFA)-3 (CD58) and immunoglobulin (Ig) G that inhibits costimulation and induces apoptosis of T cells. A 12-weeks course of alefacept 15 mg weekly was reported to significantly reduce skin symptoms, pruritus and concomitant topical steroid therapy (Simon et al. 2008). Another study demonstrated a clinical improvement in six of nine patients (Moul et al. 2008).

The anti-CD11a antibody efalizumab shown to be effective in AE by blocking the recruitment of T cells, is no longer available because of the risk of progressive multifocal leukoencephalopathy (PML). Whereas early observations stated a significant improvement upon efalizumab therapy (Takiguchi et al. 2007), a recent retrospective analysis revealed a slight effect in 5 to 11 patients only (Ibler et al. 2009). 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 suggest a pathogenic role of B cells in AE (Simon et al. 2008 rituxi). However, a report on two cases of severe AE receiving rituximab could not confirm these findings (Sediva et al. 2008).

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 (Oldhoff et al. 2005). Mepolizumab had no effect on atopy patch test reactions (Oldhoff et al. 2006). Based on the promising results in AE and the experiences in bronchial asthma therapy, long-term trials with anti-IL-5 antibodies seem indicated.

The majority of AE patients has elevated serum IgE levels, but the pathogenic role of IgE in AE remains unknown. First case reports gave inconsistent results on the effect of anti-IgE antibody (omalizumab) treatment in severe AE (Lane et al. 2006, Krathen et al. 2005). Upon low-dose anti-IgE therapy (10 cycles of 150 mg), 6 of 11 AE patients with serum IgE levels >1000 kU/l before therapy responded as shown by a decrease of SCORAD more than 50% in 2 and between 25 and 50% in 4 patients (Belloni et al. 2007). However, 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 (Heil et al. 2010). Recent studies reported, that accompanying AE significantly improved in patients receiving omalizumab because of severe bronchial asthma (Sheinkopf et al. 2008, Vigo et al. 2006, Incorvaia et al. 2008).

Anti-TNF-alpha (infliximab) has been shown to significantly decrease skin symptoms and pruritus in patients with severe AE during induction therapy (Jacobi et al. 2005). However, a sustained improvement was seen only in 2 of 9 patients during maintenance therapy (Jacobi et al. 2005). A patient with severe AE and concomitant contact allergy responded well to anti-TNF-alpha (Cassano et al. 2006). To note, some authors observed AE-like skin eruptions in patients treated with anti-TNF-alpha (Lee et al. 2007, Vestergaard et al. 2007), while others did not (Davaine et al. 2008).

None of the biologics has been approved for the therapy of AE yet. At present, the use of biologics in AE is advisable 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 as well as the costs have to be taken in account before using biologics. On the other hand, treatment with biologics provides important information on pathogenic mechanisms in AE. Today, more biologics are under investigation for treatment of allergic diseases.

Recommendations

In patients with severe AE refractory to topical and systemic treatment, a therapy with biologics (omalizumab, rituximab or alefacept) can be considered (4, C).

Allergen-specific immunotherapy (ASIT)

The efficacy of specific immunotherapy in AE has been shown in a number of case reports and smaller cohort studies (reviewed by Darsow et al. 2005, Busmann et al. 2006) and more recently in a larger multicenter trial with subcutaneous house dust mite immunotherapy (Werfel et al. 2006). Due to these data it became clear that ASIT can be applied for the treatment of allergic rhinitis or mild asthma also in those patients who suffer in addition from AE since eczema was obviously not worsened during or after ASIT. More and larger prospective studies are now being performed which shall respond to the question whether AE alone may be an indication for the initiation of ASIT. 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 (Ring 1982). 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 (review: Darsow 2005). A double-blind controlled trial of ASIT with *Dermatophagoides pteronyssinus* in children with AE was published in 1992 by Glover and Atherton. This study failed to demonstrate superiority over placebo after a standard 8-months' course of treatment with tyrosin-adsorbed house dust mite extracts in 24 children with AE and immediate hypersensitivity to this allergen. However, in a second study phase children were randomly allocated to continue with active treatment or placebo for a further 6 months. The numbers were too small to permit confident conclusions but the clinical scores suggested that prolonged hyposensitization may be more effective than placebo with regards to several objective parameters of eczema severity. The authors noted that a high placebo effect led to problems in comparing the active treatment. In the placebo-controlled study of Kaufmann and Roth (1974), the skin condition of 13 of 16 treated patients improved, whereas only in 4 of 10 placebo-treated patients this effect was noted. Similar results were reported by Warner et al. (1978) and Zachariae et al. (1985) showing improvement of eczematous skin lesions under ASIT with house dust mite extracts.

Oral ASIT for *D. pter.* was not effective in a controlled study enrolling 60 children with AE which were followed for three years (Galli et al. 1994). In contrast, Mosca et al. (1993) could show the effect of s.c. conventional ASIT (n=41; 76% improved) and sublingual route immunotherapy (SLIT; n=48; 64% improved). This study also reported on medication used and adverse drug reactions. The latter occurred in 15-20% (both groups). Mastrandrea et al. (2000,2001) reported on a 6-year-study in 35 selected AE cases undergoing SLIT, with average 72% remission of AE after 2 years. However, this observational study also lacked a control group. Pajno et al (2007) performed a controlled study applying SLIT with house dust allergens in children with AE. The outcome of this intervention was positive only in patients with mild to moderate AE but not with severe AE.

Noh and Lee (2000) reported in a pilot study 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.

Werfel et al. (2006) investigated 89 patients with AE showing a sensitization to house dust mite (CAP- $\text{FEIA} \geq 4$) 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 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 (Silny et al. 2006) under ASIT.

Even if the results of the studies are interpreted very carefully with regard to the therapeutical effects of ASIT, it is remarkable that exacerbations of the skin disease during this specific treatment were rare. In contrast, 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. One also has to keep in mind that eczema flares were seen in the control or placebo groups, too.

The role of allergens in the pathophysiology of AE has been proven in controlled studies on allergen avoidance and atopy patch testing (Darsow et al. 1997,1999; Tan et al. 1996). 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 (Darsow et al. 2005). As ASIT works in the sense of a biological response modifier, it may require a longer time to exert all its effects on inflammatory reactions as usual selected for pharmacotherapeutic trials (Mastandrea et al. 2001). The issue of combining ASIT with immunomodulating (pre-) treatment may also deserve further investigations in AE patients. So, the addition of anti-IgE treatment (with a monoclonal, commercially available antibody) to ASIT has been shown to result in increased improvement in patients with respiratory atopy (Kühr et al. 2002).

Recommendations

ASIT may have positive effects in selected, highly sensitized patients with AE. The best evidence so far is available for ASIT with house dust mite allergens (2a,B). There is no contraindication of performing ASIT in patients with respiratory allergic diseases (allergic rhinoconjunctivitis, mild allergic bronchial asthma) associated with AE (2b,B).

Complementary and alternative medicine in atopic eczema

There is evidence of growing interest of so called complimentary alternative medicine (CAM) as treatment for AE (Artik and Ruzicka 2003, Ernst et al. 1995, Happle 1998). This chapter summarises the available RCT-based evidence on specific treatment modalities.

For that purpose the electronic database PubMed was systematically searched for available randomised, controlled trials of complementary, alternative treatment modalities used for AE. The search covered the period from 1966 up to October 2009 and included the terms „atopic dermatitis or eczema“ and „complementary or alternative medicine“ as well as specific modalities such as „acupuncture, homeopathy, bioresonance, or phytotherapy“. Statements for the consensus process are given in bold letters at the end of each chapter. If not specified otherwise these are based on RCT (1a) evidence.

Definition

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” (Ernst 1995).

The underlying concept, rationale and practice of the different CAM modalities will not be described in detail. The interested reader is kindly referred to the corresponding literature (Bielory 2001).

Usage of CAM in the general population

With respect to single countries, France (49%) and Germany (46%) seem to exhibit the highest usage of CAM in Europe (Fisher et al. 1994) (Figure 1). The growing interest in CAM in the public was demonstrated by a study from the United States, indicating an increase of the usage of CAM from 33.8% to 42.1% between 1990 and 1997 (Eisenberg et al. 1998). A recently published telephone survey of the British Broadcasting Corporation revealed that 20% of a random sample of 1204 adults reported experiences with CAM in the preceding year.

Usage of CAM for AE or allergies

A few studies have investigated the patterns of use of CAM in patients with AE or related disorders. A study from Switzerland investigated 202 inpatients with atopic disorders of which 37% claimed to have used CAM previously. The most frequently used techniques were homoeopathy (48%), diet (35%) and herbalism (28%), autologous blood injection (28%), phytotherapy (20%) and acupuncture (18%) (Triebkorn and Drosner 1989).

A study from Norway investigated 444 inpatients with AE of which 51% reported the previous use of CAM. The most popular modalities were homoeopathy (34%), herbalism (19%), food supplements (18%), diet change (18%) and acupuncture (11%) (Jensen 1990).

A German population-based telephone survey in adults with allergies revealed that 26.5% have used CAM (Schäfer et al. 2002). The most common procedures were homoeopathy (35.3%), autologous blood injection (28.1%), acupuncture (16.6%) and bioresonance (10.0%).

Utilization of CAM by dermatologists

A British health service research survey compared the treatment patterns of dermatologists in Japan, the USA and the UK (Baron et al. 2002). The highest prevalence of utilization of CAM was reported by Japanese dermatologists (27%). Interestingly, dermatologists over 45 years of age prescribed CAM significantly more often in the UK and the USA.

Specific CAM modalities

Essential fatty acids

With respect to polyunsaturated fatty acids (PUFA), a distinction should be made between ω -3 acids like eicosapentaenoic acid and their metabolites and η -6 acids like arachidonic acid and the corresponding metabolites. The supplementation with η -3 fatty acids is based on the assumption that the inflammatory profile of η -6 fatty acids and their metabolites is higher than that of η -3 fatty acids and their metabolites and that the supplementation with η -3 fatty acids shifts the metabolic pathway towards less inflammatory metabolites. η -3 PUFA were studied in oral and topical administration in patients with AE. The most commonly used preparations were eicosapentaenoic acids, evening primrose oil (containing 8-10% GLA, Epogam®), borage oil (containing at least 23% GLA) and fish oil. The systematic review of treatments for AE published in 2000 summarizes available RCT evidence of supplementation with essential fatty acids (Hoare et al. 2000). The authors describe a meta-analysis of 9 RCTs (Morse et al. 1989) and another large study conducted by Bamford et al. (Bamford et al. 1985). The meta-analysis concluded that primrose oil has a modest beneficial effect. However, several trials had not been made available to the public at this stage, which made a critical methodological appraisal impossible. Results of the two largest and well reported studies on evening primrose oil could not show an effect superior to placebo. The further 9 published RCTs have given conflicting evidence. Further meta-analyses and systematic reviews on evening primrose oil and GLA supplementation are under way.

In a trial published by Ring and Kunz, 17 patients were treated with eicosapentanoic acids or placebo over 3 months (Ring and Kunz 1991). At the end, all clinical parameters had improved significantly in both with a slight superiority for placebo.

A study from India failed to show significant therapeutic effects of primrose oil 500 mg/d compared to 300mg/d sunflower oil delivered in capsules over 5 months (Senapati 2008).

Beside 4 smaller trials (Bahmer 1992, Borrek et al. 1997, Buslau 1996, Valsecchi et al. 1996), giving conflicting results, there are only two other reported RCTs on the use of borage oil in atopic eczema. In the trial published by Henz et al. (1999), 160 adult patients were treated with borage oil containing capsules or placebo over a 24 weeks period. No significant differences concerning the clinical response as a function of corticosteroid usage was found. However, sub-group analyses by centres or patients who demonstrated an increase of erythrocyte dihomo- γ -linolenic acids revealed significant results in favour of supplementation with borage oil. This might indicate a beneficial effect on those who absorb and metabolise GLA and justifies further trials.

A total of 140 patients, including 69 children, were treated by an English working group with either borage oil capsules or placebo over 12 weeks. No significant

differences in severity, symptoms, global assessment or use of medication were observed (Takwale et al. 2003).

A study from Berlin compared the daily administration of 5,4g 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 group differences were not observed (Koch et al. 2008).

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 (Callaway et al. 2005).

A recent randomised trial 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 (Mayser et al. 2002). Some smaller RCTs have also indicated a beneficial effect (Bjorneboe et al. 1987, Gimenez-Arnau et al. 1997, Bjorneboe et al. 1989), although the largest and well reported trial could show no difference between the fish oil and the placebo (Soyland 1994 et al.).

Primrose oil has also been used as topical treatment. Although the pilot study has indicated some beneficial effects (Anstey et al. 1990) further studies were unable to establish a dose response relationship (Ferreira et al. 1998). Further studies could not prove a beneficial effect on skin barrier function (Gehring et al. 1999). Large trials on that issue, however, are lacking.

Recommendations

There is not enough evidence to support the use of oral or topical applications of unsaturated fatty acids in the treatment of AE.

Phytotherapy

Herbal remedies are used either orally or topically since a long time also for skin diseases, mainly because of their anti-inflammatory and itch-relieving capacity. Detailed background information on herbal therapy in dermatology is summarized in a recent review (Bedi and Shenefelt 2002). Concerning the topical use we identified two RCTs investigating the efficacy and safety of a chamomile preparation (Patzelt-Wenzler 2000) and a cream containing hypericum extract respectively (Schempp et al. 2003). The chamomile extract containing commercial cream Kamilloosan® was compared to either 0.5% hydrocortisone cream or vehicle cream in a half side comparison in 69 patients with AE. With respect to the major outcome parameters pruritus, erythema and desquamation, Kamilloosan® was moderately superior to 0.5% hydrocortisone after a two week treatment and not different to the vehicle cream. Results of statistical analysis were not given in this publication. 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. Over 4 weeks the modified SCORAD index improved with both therapies but the improvement was significantly higher under active treatment. This promising result should be confirmed by larger trials and in comparison with topical standard therapy.

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 (Klövekorn et al. 2007). A subgroup analysis revealed superiority of the plant preparation under dry and cool weather conditions.

Plant extracts are prone to induce contact sensitisation and subsequent contact allergy. This has been studied intensively and corresponding clinical reports exist (Ernst et al. 2000, Giordano-Labadie et al. 2000). It was demonstrated that so called phytocosmetic creams containing a mixture of plant extracts also contain triamcinolone acetonide as an active ingredient (Bircher et al. 2002).

Beside negative results, there is only one RCT indicating a beneficial effect of hypericum as a topical phytotherapy. No recommendation can be given based on the available evidence.

Chinese herbal medicine

Chinese herbs are part of the traditional Chinese medicine which consists of Chinese herbs administered orally or topically, acupuncture, diet and exercise (Koo and Arain 1998, Vender 2002). Chinese herbal treatment is promoted as treatment for AE, taken orally as decoction, usually consisting of about 10 different herbs. The first randomised controlled trials of Chinese herbal medicine in the treatment of AE outside China were published by Sheehan and co-workers in 1992 (1992 BJD, 1992L) and subsequently summarised in a systematic review (Armstrong and Ernst 1999). In a similar cross-over design, 37 children and 31 adults received either an active or a placebo plant mixture over an 8-week period. The severity scoring included erythema, surface damage and percentage area affected. The median percentage change for surface damage in the children's group was 63.1% for Chinese herbs, compared with 6.2 % for placebo. In a one-year follow-up the 23 children who decided to stay on Chinese herbs showed overall better results than those who quit this therapy (Sheehan et al. 1994). In the adult group the geometric mean for surface damage at the end of Chinese herbs treatment was 11.3 compared with 111 at the end of placebo (Sheehan et al. 1995). After one year 12 of the 17 adults, who decided to continue the herbal treatment had a greater than 90% reduction in the clinical score which was significantly better than those of the 11 patients, who chose not to carry on taking the medication. Short term toxicity was not observed in these trials but prior routine checks of haematological, renal and hepatic function were recommended. Serious adverse effects including fatal hepatitis have been reported by independent investigators following these trials (Koo and Arain 1998, Mostefa-Kara 1992, Wang and Lu 1992, Perharic et al. 1995). A further trial investigating a commercial product of Chinese herbs (Zemaphyte®) focused on immunological outcomes and indicated relevant immunological as well as clinical effects (Latchman et al. 1996). Zemaphyte was further evaluated and compared to placebo in a cross-over trial involving 37 patients (Fung et al. 1999). A trend towards clinical improvement was observed in both groups without significant differences between groups.

The oral application of a combination of *Eleutherococcus*, *Achillea millefolium*, and *Lamium album* was not superior to placebo after two weeks (Shapira et al. 2003).

Although earlier reports indicated beneficial effects of Chinese herbal medicine in the treatment of AE, consecutive trials could not confirm these findings and further studies including larger sample sizes are certainly needed.

Recommendations

There is not enough evidence to support the use of Chinese herbs in the treatment of AE.

Acupuncture

Acupuncture has not been studied 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 (Chung-Jen and Hsin-Su 2003, Adaskevich 2000, Pfab et al. 2010).

Recommendations

There is absence of evidence to support the use of acupuncture in the treatment of AE.

Autologous blood therapy

We located one RCT comparing the re-injection of 1 to 3 ml autologous blood over 5 weeks to the injection of the equivalent amount of sterile saline solution (Pittler et al. 2003). Patients were recruited via press advertisement and finally 30 subjects participated. Over a 9 weeks period, eczema severity as 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 severity score. This finding should be confirmed in larger trials and different settings.

Recommendations

There is no evidence to support the use of autologous blood therapy in the treatment of AE.

Bioresonance

One RCT has been published so far, comparing bioresonance with a sham procedure in 36 children with AE attending a specialized rehabilitation unit in Davos, Switzerland (Schoeni et al. 1997). After 4 weeks, severity score has improved in both groups with slight superiority of the active group (differences 12.5 vs. 8.7). Statistical significant differences between groups did not occur. Although small benefits cannot be excluded, this study could not demonstrate a substantial clinical effect and further studies under more usual out-patient conditions are needed.

Recommendations

There is no evidence to support the use of bioresonance in the treatment of AE.

Homoeopathy

Large case series illustrating the therapeutic benefits have been published as papers or books (Ernst 2000, Eichler and Frank 2002). A recent uncontrolled trial of 17 patients with longstanding AE in Japan revealed a marked improvement after the

introduction of homoeopathic treatment (Itamura and Hosoya 2003). A classical randomised placebo controlled trial was initiated in Germany including 60 patients (Remy et al. 1995). There was no difference between placebo and verum homeopathy in the outcome of AE (Siebenwirth et al. 2009).

Recommendations

There is absence of evidence to support the use of homeopathy in the treatment of AE.

Massage therapy / aroma therapy

The effect of additional massage therapy applied daily for 20 minutes over a one month period compared to standard therapy alone was investigated in a randomised trial in 20 children (Schachner et al. 1998). 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 (Anderson et al. 2000). 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.

Recommendations

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

Salt baths

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 (Halevy et al. 1998, Harari et al. 2000). A large clinical observation of 1408 patients with AE, who stayed 4-6 weeks in the Dead Sea area revealed complete clearance of lesions in 90% of the patients (Shani 1997).

In another study from the Dead Sea area of 56 patients with AE, bathing in diluted Dead Sea water was compared with bathing in sweet water (20 minutes, twice a day) as part of the climatotherapy regimen. As a result the severity index improved significantly in both groups without significant differences between groups (Giryas et al. 1997).

Another uncontrolled trial investigated the use of narrow band UVB and bathing in Dead Sea salt solution. Significant improvement according to the SCORAD score was reported in per-protocol analysis (N=143) or intention to treat analysis (N=615) (Schiffner et al. 2002). In a small trial from Germany, 12 patients were treated with UVA/B monotherapy and compared to 16 patients who underwent UVA/B phototherapy plus salt water baths (Dittmar et al. 1999). After 20 treatments, the SCORAD score improved markedly and significantly in the balneophototherapy group

and only a marginal improvement was observed in the UVA/B monotherapy group. The patients of this small trial however were not randomised and the baseline severity indicates that SCORAD of the patients in the combination therapy group was much higher. In another German trial, Dead Sea salt bath plus phototherapy were compared with salt bath alone (Zimmermann and Uterman 1994). However, results of the 8 patients included with AE were not given separately.

In a randomised trial from Japan, 100 patients were assigned to get either Deep Sea water or physiological saline sprayed on the skin every for 10 minutes, every day for one week (Adachi 1998). Clinical improvement was small in both groups and not statistically different.

Recommendations

At the moment there is not enough RCT evidence to support the use of salt baths in the treatment of AE.

Vitamins and minerals

A total of 6 trials were identified investigating vitamins or minerals in the treatment of AE (Czeizel and Dobo 1994, Fairris et al. 1989, Hakagawa and Ogino 1989, Mabin et al. 1995, Tsourelis-Nikita et al. 2002, Sidbury et al. 2008). A recent study from Italy studied 96 patients who were randomised to either 400 IU of vitamin E taken orally once a day, or placebo over the period of 8 months (Tsourelis-Nikita et al. 2002). According to the subjective assessment of the clinical outcome after 12 months, marked differences between groups were observed. A great improvement was reported by 46% in the vitamin E group, compared to only 2% in the placebo group and correspondingly, 87% of the placebo group reported worsening and 8% did so in the vitamin E group. Unfortunately results of statistical tests are not given in the publication. 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 (Hakagawa et al. 1989).

A further trial in 60 adults with AE compared selenium or selenium plus vitamin E vs. placebo over a 12 weeks period (Fairris et al. 1989). 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 (Czeizel and Dobo 1994). 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 (Ewing et al. 1991). The severity score increased in both study groups without significant differences.

There is one published RCT comparing pyridoxine (vitamin B₆) vs. placebo in 41 children over a 4 weeks period (Mabin et al. 1995). 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.

In the only pilot study on Vitamin D so far, 5 children were treated daily with 1000 IU for one month. Compared to 6 controls the EASI score improved, but without statistical significance (Sidbury et al. 2008).

Recommendations

There is preliminary evidence that vitamins, especially vitamin E and D, are useful in the treatment of AE but further trials are needed before an evidence based recommendation can be given.

Topical Vitamin B12

There are two smaller studies with half-side comparisons, which indicate a beneficial effect of a preparation containing 0.07% vitamin B12 in avocado oil compared to a placebo preparation. After application over 8 weeks in 41 adults the modified SASSAD score dropped significantly more in the verum area. Similar, the global patients and physicians assessments were significantly better for the area which was treated by verum in this German study (Stücker et al. 2004). In the US the preparation was tested in a similar design in 21 children and showed a significant superiority over placebo with respect to the SCORAD (Januchowski 2009). Large scale studies should follow to confirm these results.

Recommendations

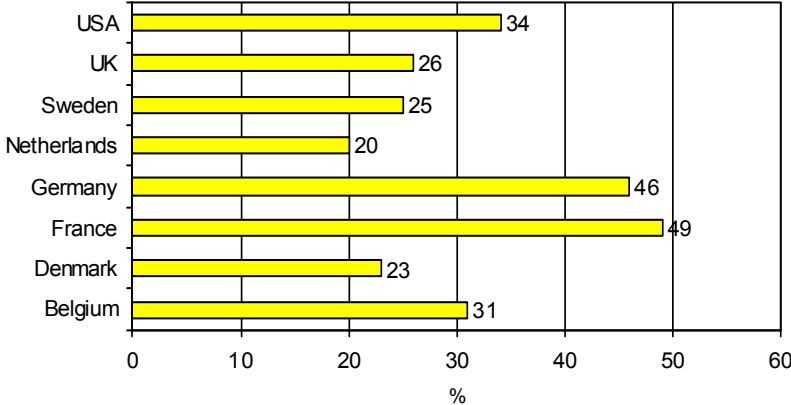
The committee feels that these studies do not provide enough evidence in order to recommend this treatment.

Harms

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.

Figure 1

Results from population-based studies reporting use of complementary medicine in the USA and selected European countries (acc. to P Fisher & A Ward 1994)



Psychosomatic counseling

Psychological and emotional factors are well known to influence the clinical course of AE, which is reflected by the name “neurodermitis” in some countries for this disease. The itch-scratch cycle is especially vulnerable to psychological influences and can show a tendency to self-perpetuation (Raap et al. 2003, Gieler 2006, Koblenzer and Koblenzer 1988).

It is also known that stress can elicit severe exacerbations of eczematous skin lesions (Kupfer et al. 2001).

At the same time psychosomatic disease in the sense of anxiety or depression can be co-morbidity features of AE (Gieler 2006).

Quality of life is severely impaired in AE patients (Finlay 1996).

Therefore a variety of psychotherapeutic approaches including psychosomatic counseling and behavioural therapy have been studied.

Two randomized controlled trials compared the use of topical corticosteroid alone with steroids together with a behavioural therapy program which led to a significantly pronounced improvement of skin condition and itch-scratch behavior (Noren & Melin 1989).

Autogenic training together with cognitive behavioural therapy was studied in a standardized educational program (see chapter “Education”) (Ehlers et al. 1995).

Behavioural therapy against itch was studied by Niebel (1990) showing a significant improvement in symptoms after one year.

Psychosomatic counseling and psycho-education with regard to relaxation techniques and behavioural therapeutical programs are part of several educational programs used in AE (see “Education”).

Intrafamilial psychodynamics are also well-known factors influencing the clinical course of AE (Gieler & Effendy 1984, Ring & Palos 1986).

Most psychological training programs include relaxation techniques, 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.

Recommendations

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

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

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

Educational Interventions for Atopic Eczema

Psychological and educational interventions enhance the effectiveness of conventional therapy for children with AE. These interventions are focused on the process of acquiring new knowledge, or skills through teaching and learning activities. Information and formal teaching lead the recipients to become more accurately informed about the condition, and therefore better equipped to understand the need for medical treatments and good disease management. This improvement in disease control will restore family dynamics, the patient and family will cope better and have an overall improvement in quality of life. Additionally, education should aim to reduce doctor's visits, facilitate a better partnership between the doctor, and the patient, parent. This leads to a decrease of the long-term costs of chronic disease treatment.

Educational service delivery models

There are different educational programs running all around the world. These differ in number and certification of the educator, number of participants, age of patients, duration and frequency of interventions. The outcome of the patient education depends on the education techniques, the skills of the educator, and the composition of the participants.

Multidisciplinary age related structured group training educational programs: There is evidence that structured age related programs are significantly improving severity score, improving coping behavior, parents handling their affected children, increasing disease knowledge. (Staab et al. 2006, Grillo et al. 2006, Evers et al. 2009, Weisshaar et al. 2008, Kupfer et al. 2010).

Eczema workshops: Significantly more patients from the eczema workshop improve from moderate to mild severity score (Moore et al. 2009, Darsow et al. 2010). There is greater adherence to eczema management (coping behavior, parent's handling their effected children) in the eczema school, compared with the standard dermatologist-led clinic (Kupfer et al. 2010).

Atopic eczema educator: There is no evidence that this kind of intervention improves the severity, the quality of life, or the disease outcome. Itch-scratching cognitions are improving and parents deal with their effected children better. The additional psychological benefit in the training group does not only depend on the greater improvement of SCORAD values, the disease knowledge is increasing (Shaw et al. 2008, Kupfer et al. 2010, Ricci et al. 2009).

Nurse-led eczema workshops, single nurse-led interventions, nurse-led care: The self management techniques are improving. There is evidence, that the benefits of nurse interventions are the reduction in the severity of the condition and the use of topical therapies are more effective. There is a reduction in referrals to the general practitioner or dermatologists, and the disease knowledge is increasing (Courtenay et al. 2006, Moore et al. 2009, Kupfer et al. 2010).

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, small improvement in psychological well-being, there was no difference in quality of life (Foster et al. 2007).

No evidence that such programs improve psychological health (Van Os-Medendorp et al. 2007, Cork et al. 2003, Laurant et al. 2004).

Forms of educational intervention tools

There are numerous kinds of intervention tools, which help to improve understanding, and knowledge. The different health systems have different backgrounds (Smidt 2007, Williams et al. 2006).

There is evidence that a special educational school enhances better knowledge of the disease, and has positive effects (Radulescu et al. 2007, Gore et al. 2005, Haubrock et al. 2009).

There is no evidence that demonstrations, lectures, question and answer sessions, relaxation techniques result in significant improvement of disease severity (Ersser 2007). The patient's perceptions of conventional medicine with medical expert with good communication skills is improved (Norreslet 2009).

Direct telephone access to a nurse lead to a better understanding of self management (Gore et al. 2005).

Video-based education, films, audiotapes, books booklets, leaflets, handouts, questionnaires improve the disease knowledge, but the evidence of usefulness needs further investigation (Barbarot et al. 2007, Agner et al. 2005, Holm et al. 2005, Gieler et al. 2000).

There are no available controlled clinical trials in case of the use of written action plans (WAPs), the effect on adherence in pediatric AE needs further investigation (Chisolm 2008, Gore 2005).

Website information for educating patients is not sufficient, because the internet is not generally accessible. Internet access is not common everywhere and the information is not necessarily credible among adult patients. The actual status needs further investigations in each country (Stalder and Barbarot 2006, Asai et al. 2006).

The health systems and possibilities are differing in each countries. Personal contact, and the structured programs such as the educational schools show the most benefit.

Recommendations

Educational programmes (training programmes, "eczema schools") for AE in children and adults are highly efficient and established already in many countries. The multidisciplinary age related structured group training educational programs are improving coping behavior, parents handling their children. The skin symptoms improve, and there is less need for medicaments. These programs have the most benefit and are therefore recommended as an adjunct to conventional therapy of AE (1a, A).

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

The nurse led programs result in more effective use of topical therapies and improvement in severity scores, but there is a narrow range in their roles, though it is remarkable that this intervention is sparing doctor's time (2a, 2b B).

There is no evidence of change in severity scores due to the programs led by an AE educator, nor the lay-led self management education programs, which have weak effect in improvement, but the disease knowledge is increasing (-, D).

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