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GUIDELINES

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

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Abstract

This guideline was developed as a joint interdisciplinary European project, including physicians from all relevant disciplines as well as patients. It is a consensus-based guideline, taking available evidence from other guidelines, systematic reviews and published studies into account. This second part of the guideline covers antimicrobial therapy, systemic treatment, allergen-specific immunotherapy, complementary medicine, psychosomatic counselling and educational interventions, whereas the first part covers methods, patient perspective, general measures and avoidance strategies, basic emollient treatment and bathing, dietary intervention, topical anti-inflammatory therapy, phototherapy and antipruritic therapy. Management of AE must consider the individual clinical variability of the disease. Systemic immunosuppressive treatment with cyclosporine, methotrexate, azathioprine and mycophenolic acid is established option for severe refractory cases, and widely available. Biologicals targeting the T helper 2 pathway such as dupilumab may be a safe and effective, disease-modifying alternative

when available. Oral drugs such as JAK inhibitors and histamine 4 receptor antagonists are in development. Microbial colonization and superinfection may cause disease exacerbation and can require additional antimicrobial treatment. Allergen-specific immunotherapy with aeroallergens may be considered in selected cases. Psychosomatic counselling is recommended especially in stress-induced exacerbations. Therapeutic patient education ('Eczema school') is recommended for children and adult patients. General measures, basic emollient treatment, bathing, dietary intervention, topical anti-inflammatory therapy, phototherapy and antipruritic therapy have been addressed in the first part of the guideline.

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Conflicts of interest

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

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Abbreviations

AAD: American Academy of Dermatology
AD: atopic dermatitis
AE: atopic eczema
AEGIS: 3-trimethylsilylpropyl-dimethyloctadecyl ammonium chloride
AGREE: appraisal of guidelines research and evaluation
AH: antihistamines
APT: atopy patch test

ASIT: allergen-specific immunotherapy
AZA: azathioprine
BB-UVB: broadband ultraviolet B
BCC: basal cell carcinoma
BO: borage oil
CAM: complementary alternative medicine
CAP-FEIA: CAP fluorescence immunoassay
CHM: Chinese herbal medicine
DBPC: double-blind placebo-controlled
DBPCFC: double-blind placebo-controlled food challenge
DHA: docosahexaenoic acid
EADV: European Academy of Dermatology and Venereology
EASI: eczema area and severity score, a signs score
EAT: enquiring about tolerance
EC: eczema coxsackium
EC-MPS: enteric-coated mycophenolate sodium
EDF: European Dermatology Forum
EFA: European Federation of Allergy and Airways Diseases Patients' Associations
EH: eczema herpeticum
EPO: evening primrose oil
ETFAD: European Task Force on Atopic Dermatitis
EU: European Union
EV: eczema vaccinatum
FA: food allergy
FTU: fingertip unit
GAAPP: global allergy and asthma patient platform
H1R: histamine 1 receptor
HBD: human-ß-defensin
HDM: House Dust Mite
HTA: health technology assessment
IA: immunoadsorption
ICAM1: intercellular adhesion molecule 1
IFN-γ: interferon gamma
IFN-α: interferon alpha
IGA: Investigators Global Assessment, a signs score
IgE: immunoglobulin E
IgG: immunoglobulin G
IL: interleukin
IVIG: intravenous immunoglobulins
JAK: Janus kinase
LEAP: learning early about peanut allergy
LTC4: leukotriene C4
LTD4: leukotriene D4
LTE4: leukotriene E4
MCV: molluscum contagiosum virus
MMF: mycophenolate Mofetil
mTLSS: modified Total Lesion Symptom Score
MTX: methotrexate
NB-UVB: narrow band ultraviolet B
OFC: oral food challenge
OTC: over the counter
PDE 4: phosphodiesterase 4
PE: patient education
PO-SCORAD: patient-oriented scoring of atopic dermatitis
PUVA: psoralen and ultraviolet A
QoL: QUALITY of life
RCT: randomized controlled trial
ROS: reactive oxygen species
SASSAD: six area six signs atopic dermatitis score
SCC: squamous cell carcinoma
SCIT: subcutaneous immunotherapy
SCORAD: scoring of atopic dermatitis, a composite score
SLIT: sublingual immunotherapy
SPT: skin prick test
TCI: topical calcineurin inhibitors
TCS: topical corticosteroids
Th1: T helper 1 cells
Th17: T helper 17 cells
Th2: T helper 2 cells
TPMT: thiopurine methyltransferase
TSH: thyroid-stimulating hormone
TSLP: Thymic stromal lymphopoietin
UV-light: ultraviolet light
VOCs: volatile organic compounds
VZV: Varicella-zoster Virus

Table of contents

For a detailed description of the methods used in this guideline (See also Tables 1-3), refer to part I of the guideline.

Antimicrobial therapy

In patients with AE, the inflammatory micro-milieu initiated by TSLP, IL-4 and IL-13 may downregulate the cutaneous antimicrobial peptides such as cathelicidin LL-37, dermcidin, human

β-defensins HBD-1, HBD-2 and HBD-3.[1,2] This is one of the reasons why these patients are more susceptible to secondary skin infections, which tend to generalize.[2] The understanding of colonization and infection in AE has largely increased by structured investigation of the human microbiome in the context of AE. Flares of AE are significantly associated with a *Staphylococcus aureus*-caused loss of diversity in the cutaneous microbiome, which is not significant if patients have followed a proactive therapy regimen before the flare.[3]

Antibacterial

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

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

Underestimated sources of bacteria are cream and ointment containers, of which up to 53% are contaminated, up to 25% with *S. aureus*. Thus, the following recommendations seem to be useful[14]: (i) keep open moisturizers in refrigerator; (ii) use pumps or pour bottles rather than jars; (iii) avoid direct contact with hands and decant; (iv) avoid sharing personal hygiene items.

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

Antiviral

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

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

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

Molluscum contagiosum virus (*MCV*) infection is in general benign and self-limited, but in patients with AE dissemination is frequent and therefore treatment is recommended. A large variety of topical treatments have been reported such as cantharidin, potassium hydroxide, tretinoin cream, topical cidofovir and others.[27] Physical therapies including cryotherapy and curettage are also effective, but not always well tolerated in paediatric patients.[28] Topical treatment of AE with TCS may be continued during MCV infection.

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

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

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

Antifungal

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

Summary of evidence

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

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

Topical glucocorticosteroids and calcineurin inhibitors reduce the colonization rate of *S. aureus* in AE.

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

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

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

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

Recommendations

- A short course of systemic antibiotics, such as cephalosporin, may be considered in AE patients clinically infected with *S. aureus*. (2b, B)
- The long-term application of topical antibiotics is not recommended due to the risk of increasing resistances and sensitizations. (2, D)
- Treatment with topical antiseptic drugs – including antiseptic baths e.g. with diluted sodium hypochlorite – should be considered, if clinical signs of bacterial superinfection are present. (4, C)
- Treatment with topical antiseptic drugs – including sodium hypochlorite 0.005% baths – may be considered in patients with treatment-resistant, chronic course of AE. (2b, B)
- Eczema herpeticum should be treated without delay using systemic antiviral therapy, such as systemic aciclovir. (4, D)
- VZV vaccination is recommended for children with atopic dermatitis. Parents of atopic children should be encouraged to fully immunize their children. (2a, B)
- Topical or systemic antifungal therapy may be effective in some AE patients, mainly in those suffering from the 'head and neck' variant of AE or with demonstrated IgE sensitization to *Malassezia* spp. (2b, B)

Systemic anti-inflammatory treatment

Immunosuppressive treatment

Oral glucocorticosteroids

Oral glucocorticosteroids are used in many Europeancountries for treatment of AE. Well-known side-effects limit their use especially for long-term treatment (see Table 4). Funding of expensive clinical trials in the near future is unlikely.

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

Summary of evidence

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

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

Recommendations

- Short-term (up to 1 week) treatment with oral glucocorticosteroids may be an option to treat an acute flare in exceptional cases of AE. Restrictive use, largely limited to adult patients with severe AE, is recommended. (−, D)
- The daily dose should be adjusted to and not exceed 0.5 mg/kg bodyweight. (−, D)
- Long-term use of oral glucocorticosteroids in AE patients is not recommended. The indication for oral steroids in children should be handled even more cautiously than in adults. (−, D)

Cyclosporine A

Cyclosporine is licensed in many European countries for treatment of AE and is therefore considered to be the first-line option for patients with severe disease who require systemic immunosuppressive treatment (see Figure 1).

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

Cyclosporine dose finding study for AE treatment in adult patients. A fixed-dosage cyclosporine regimen was evaluated in 106 adults with severe AE.[43] Initial treatment was performed with 300 mg/day or 150 mg/day and reduced after 2 weeks to 50% of the initial daily dose until a final evaluation was performed after 8 weeks. Clinical efficacy was detectable after 2 weeks in both treatment groups, but the higher dose was significantly more effective ($P < 0.05$). The authors recommended to start therapy with 150 mg/day, because this regimen showed a lower incidence of serum creatinine increase. It is recommended today to start with a higher dose of 4–5 mg/kg/day to obtain a good initial result unless the patient is old or suffers from relevant concomitant diseases.[44] Some patients may tolerate low-dose cyclosporine therapy for a longer time than the usually recommended therapy length of 2 years.[45]

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

Cyclosporine or UV therapy for AE. Cyclosporine was tested against a combined UV/UVB regimen in a 1 year, open-label, multicentre trial involving 72 patients.[47] Cyclosporine therapy induced a significantly higher number of days in remission, as compared to UV therapy.

Compounding of cyclosporine. Micro-emulsions of cyclosporine show an earlier onset and higher peak value of efficacy compared to traditional formulations.[48] The clinical efficacy evaluated after 8 weeks of therapy was, however, identical for both formulations.

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

Summary of evidence

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

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

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

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

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

Recommendations

- Cyclosporine may be used in chronic, severe cases of AE in adults. Treatment should not exceed a 2-year continuous regimen. Careful monitoring for potential severe side-effects must be performed. (1a, A)
- Cyclosporine may be used (off label) in children and adolescent patients showing a refractory or severe course of disease. A detailed patient monitoring, especially of the renal status, is advisable. (2b, B)
- The duration of cyclosporine therapy is guided by clinical efficacy and tolerance of the drug. Both short-term and long-term therapies may be useful in AE. (−, D)
- Common side-effects of cyclosporine (e.g. nephrotoxicity, hypertension) argue against a long-term treatment of AE with cyclosporine. Therefore, an interval of 3–6 months is usually recommended. (−, D)
- Cessation of therapy or switch to another systemic drug should be attempted after 2 years of therapy, although many patients tolerate much longer therapy with low-dose cyclosporine. (−, D).
- An initial daily dose of 5 mg/kg/day, divided upon two single doses, is recommended. A dose reduction of 0.5–1.0 mg/kg/day every 2 weeks is recommended, once clinical efficacy is reached. (−, D)
- Dose reduction should be considered according to clinical efficacy. Long-term treatment prescribing the lowest clinically useful dose may be advisable in selected cases. (−, D)
- Since an intermittent-dosage regimen (e.g. 'weekend therapy') will lead to lower cumulative doses of cyclosporine and is effective in some AE patients, an individualized dosage regimen is recommended for underage patients. (−, D)
- Cyclosporine trough levels do not need to be assessed routinely during therapy. (−, D)
- Although there are no controlled studies available regarding the efficacy of vaccination during cyclosporine therapy, there is no evidence for a failure during cyclosporine either. Hence, a cessation of therapy of 2 weeks before and 4–6 weeks after vaccination may be advisable. Clinically, there is no evidence for this recommendation. (−, D)
- A combination therapy of cyclosporine with UV therapy is not recommended, and effective UV protection should be used. (−, D)

Azathioprine (AZA)

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

Controlled clinical trial data demonstrating efficacy Efficacy of AZA was tested in a randomized, controlled, 6-month, crossover clinical trial involving 37 patients aged 17–73 years.[49] The drop-out rate was high (12 patients on AZA, 4 patients on placebo). AZA (2.5 mg/kg/day) or placebo was given for 3 months each in a crossover design. The SASSAD skin severity score was reduced by 26% in the AZA group and 3% in the placebo group ($P < 0.01$). Pruritus, sleep loss and fatigue improved significantly during AZA, but not during placebo treatment.

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

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

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

A retrospective, uncontrolled study investigated 48 children and adolescents aged 6–16 years diagnosed with severe AE.[53] After 3 months of therapy, 28 patients showed very good and 13 patients showed good improvement of their symptoms, while seven 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 2 mg/kg/day AZA, and the dose was increased to 3 mg/kg/day in 14 patients due to insufficient clinical response. The mean time to achieve clinical response was 4 weeks.

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

Safety profile of azathioprine The authors of the Berth-Jones study concluded that AZA would be an effective and clinically

useful drug for treatment of severe AE, but would be associated with a high rate of unwanted drug effects.[49] Leucocyte counts and liver enzymes must be controlled during therapy. The higher dose caused gastrointestinal symptoms in 14 patients; leukopaenia in two and elevated liver enzymes in eight patients. Long-term efficacy and safety data in AE patients are sparse, but AZA increased the risk of non-melanoma skin cancer and lymphoma in inflammatory bowel disease patients.[55]

Summary of evidence

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

One small prospective clinical trial in children showed efficacy of AZA.[4]

Recommendations

- AZA may be used (off label) in adult AE patients, if cyclosporine is either not effective or contraindicated. (1b, A)
- AZA may also be used (off label) in children. (4, C)
- Patients should be screened for TPMT activity before starting AZA therapy to reduce the risk for bone marrow toxicity by dose adaptation. The suggested dose range is 1–3 mg/kg bw/day. (1b, A)
- Alternatively, an initial AZA dose of 50 mg/day in adults and a slow increase in the dose under close monitoring of full blood and liver function count is possible. (−, D)
- In pregnant women, AZA should only be used on strict indication. (−, D)
- AZA should not be combined with UV therapy, and effective UV protection should be used. (−, D)

Mycophenolate mofetil

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

Table 1 Grades of evidence

1a)	Meta-analysis of randomized clinical trials (RCTs)
1b)	Single RCTs
2a)	Systematic review of cohort studies
2b)	Single cohort studies and RCTs of limited quality
3a)	Systematic review of case–control studies
3b)	Single case–control study
4)	Case series, case cohort studies or cohort studies of limited quality

Recommendations (see Table 2) were classified based on the grade of evidence.

Table 2 Classification of strength of recommendation

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

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

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

Summary of evidence

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

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

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

Recommendations

- MMF may be used (off label) for treatment of AE in adults in a dose up to 3 g/day, if cyclosporine is not effective or not indicated. (4, C)
- MMF may be used for treatment of AE in children or adolescents. (4, C)
- As MMF and EC-MPS are both teratogenic, men and women of childbearing potential must use effective contraception during therapy. (3a, B)

Methotrexate (MTX)

The immunosuppressant MTX is frequently used in psoriasis, but there are little published data on its use in AE. Some clinicians have used this drug in AE with good responses since many years. MTX can be given by oral, intravenous or subcutaneous

Table 3 Language of recommendations

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

Table 4 Systemic drugs for treatment of severe atopic eczema

	Cyclosporine	Methotrexate	Azathioprine	Mycophenolic acid	Corticosteroids	Dupilumab
Overall recommendation	++ acute flare intervention	++ long-term maintenance	Can be used long term	++ little toxicity	Outdated‡	Long-term maintenance
Time to respond (weeks)§	2	8–12	8–12	8–12	1–2	4–6
Time to relapse (weeks)	<2	>12	>12	>12	<2	>8
Most important side-effects	Serum creatinine ↑ blood pressure ↑	Haematological liver enzymes ↑ gastrointestinal	Haematological liver enzymes ↑ gastro-intestinal	Haematological skin infections gastro-intestinal	Cushing's osteoporosis diabetes	Conjunctivitis
Starting dose adult	4–5 mg/kg/day‡	5–15 mg/week	50 mg/day‡	MMF 1–2 g/day (EC-MPA 1.44 g/day)	0.2–0.5 mg/kg/day	600 mg loading dose
Maintenance dose adult	2.5–3 mg/kg/day	Most often 15/week; can increase to max 25 mg/week	2–3 mg/kg/day†	MMF 2–3 g/day (EC-MPA 1.44 g/day)	Not for maintenance‡	300 mg/2 weeks
Starting dose children	5 mg/kg/day	10–15 mg/m^2/week	25–50 mg/day	MMF 20–50 mg/kg/day	0.2–0.5 mg/kg/day	No data yet
Maintenance dose children	2.5–3 mg/kg/day	Increase 2.5–5 mg/week, decrease 2.5 mg/week to effective/lowest effective dose	2–3 mg/kg/day†	Increase daily total dose by 500 mg every 2–4 weeks up to 30–50 mg/kg/day	Not for maintenance‡	No data yet
Pregnancy	Possible	Teratogenic, absolutely contraindicated	Conflicting data, possible with strict indication	Teratogenic, absolutely contraindicated	Possible	No data yet
Fathering	Possible	Little information, conflicting data, contra-indicated	Little information, possible with strict indication	Conflicting data	Possible	No data yet

†TPMT heterozygote 1–1.5 mg/kg/day. ‡See full text. §Time to reach most of expected full response.
EC-MPS, enteric-coated mycophenolic sodium; MMF, mycophenolate mofetil.

application. Funding of expensive clinical trials in the near future is unlikely.

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

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

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

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

Table 5 Upcoming systemic drugs for treatment of atopic eczema

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

†See full text.

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

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

Summary of evidence

An open, uncontrolled clinical trial, as well as broad clinical experience, indicates that MTX may be effective in AE.[4]

MTX is a teratogenic substance. (3a)

Recommendations

- MTX may be used (off label) for treatment of AE in both adults and children. (4, C)
- The recommended dosing regimen is similar or slightly lower compared to psoriasis. (D, −)
- As MTX is teratogenic, men and women of childbearing potential must use effective contraception during therapy. (3a, B)

Biological agents

Biological agents (biologics) have been used in dermatology for more than 10 years for other inflammatory skin diseases, especially psoriasis, but so far only one registered biologic for AE is available in Europe. Biologics present a relatively new group of therapeutics created by using biological processes that include recombinant therapeutic proteins such as antibodies or fusion proteins. Biologics specifically target inflammatory cells and/or mediators, respectively. In AE, biologics may be helpful in reducing inflammation by modulating the number, activation and function of immune cells or the action of cytokines or disease relevant antibodies. Several case reports, pilot studies and retrospective analyses on the effect of biologics in patients with moderate-to-severe AE refractory to topical and/or systemic therapy have been published, and randomized, placebo-controlled studies evaluating the efficacy and safety of a few biologics in AE are now available.

Approved biologic therapy

Dupilumab Dupilumab, a fully human monoclonal antibody that blocks the common α-chain of the receptor for interleukin-4 and interleukin-13, has been approved as first-line treatment for moderate-to-severe adult AE in the USA in March 2017 and in Europe in September 2017. Dupilumab has previously shown efficacy in patients with asthma and elevated eosinophil levels and now also in AE.[65] Randomized, double-blind, placebo-controlled trials involving adults who had moderate-to-severe AE were performed. In 4-week monotherapy studies, dupilumab resulted in rapid and dose-dependent significant improvements in pathophysiological and clinical parameters. Side-effect profiles were not dose-limiting, and mostly mild side-effects were observed. In a 12-week double-blind study where topical corticosteroids were combined with dupilumab or placebo, the group treated with dupilumab had significantly better effect on both AE activity and pruritus.[65] The positive outcome for dupilumab-treated moderate-to-severe adult AE patients was confirmed in a double-blind, placebo-controlled study involving 380 randomly assigned to different dosages of dupilumab or placebo.[66] Recently, the two identical phase III SOLO studies in adults have completed the clinical development programme for dupilumab, again confirming the efficacy of dupilumab monotherapy on skin signs and symptoms, and overall improvement of the QoL in AE. A significant proportion of patients achieved an IGA score of clear and almost clear and at least a 75% improvement in EASI score.[67] The LIBERTY AD CHRONOS studies indicate

maintenance of efficacy over 1 year of continued treatment with dupilumab.[68] The safety profile of dupilumab was good, with conjunctivitis being the only adverse event that was observed more frequently with dupilumab than with placebo. In view of all trials published so far, about 1/3 of all treated patients are clear or almost clear in IGA from their AE. Up to 70% of patients achieve an EASI 75 or higher skin improvement, and it takes about 4 weeks to reach the full clinical outcome. Skin signs, QoL and symptoms including pruritus significantly improved as early as 2 weeks after treatment initiation. Several ongoing studies involving both children and adolescents will show if these subgroups of the AE population may experience equally positive effects, expanding the treatment indication for dupilumab even further.

Summary of evidence

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

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

Recommendations

- Dupilumab is recommended as a disease-modifying drug for patients with moderate-to-severe AE, in whom topical treatment is not sufficient and other systemic treatment is not advisable. (1, a)
- Dupilumab should be combined with daily emollients and may be combined with topical anti-inflammatory drugs as needed. (2, b)

Upcoming biologic therapy

Nemolizumab Nemolizumab, a humanized monoclonal antibody directed against the IL-31 receptor A, has shown efficacy in patients with moderate-to-severe AE.[69] There was a significant improvement in the primary endpoint pruritus, as well as in the objective signs of the AE with, however, less efficacy. Nemolizumab is currently not approved for any indication (see Table 5).

Summary of evidence

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

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

Off-label use of other traditional biologicals

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

Mepolizumab Inflammation in AE is characterized by a T helper 2 cytokine expression including interleukin (IL)-5 and eosinophil infiltration. Upon short-term therapy with the anti-IL-5 antibody mepolizumab (2 × 750 mg), a moderate improvement of clinical symptoms was observed, although a rapid depletion of eosinophils in the peripheral blood was noted.[72] The patients were not stratified for eosinophilia in this study. Mepolizumab had no effect on atopy patch test reactions.[73] Based on the promising results in AE and the experiences in bronchial asthma therapy, long-term trials with anti-IL-5 antibodies are now performed.

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

Ustekinumab By blocking IL-12 and IL-23, ustekinumab can regulate Th1, Th17 and also Th22 pathways, which are reportedly active in AE. Results regarding the use of ustekinumab in severe AE have, however, been conflicting and only case reports have been published so far. Some have reported significant improvement of AE,[83] and some have not.[84] The first two randomized controlled trials comprising 79 and 33 patients in total

have been completed, and results are quite uniform showing no significant decrease in severity scores.[85,86]

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

On the other hand, a number of highly interesting substances are in progress and may soon be registered for treatment of AE. Therefore, the committee decided to produce a table in the addendum on potential new biologics or small molecules for AE 'in the pipeline', which will be continuously updated by the guideline committee (Table 5). Substances to be included in this table will be, among others, the anti-IL-13 antibody tralokinumab, the anti-TSLP antibody tezepelumab and the Janus kinase (JAK) inhibitor upadacitinib.

Summary of evidence

None of the traditional biologics has been approved for the therapy of AE in Europe. At present, the use of traditional biologics in AE should be tried only in patients with severe AE refractory to other topical and/or systemic treatment. Besides the lack of efficacy and safety data in AE, the potential side-effects must be taken into account before using biologics. On the other hand, treatment with biologics may provide important information on pathogenetic mechanisms in AE. Today, the imminent availability of Th2-blocking biologics has further reduced the clinical need for experimental therapy with traditional biologics. (−)

Recommendations

- A therapy of AE with traditional biologics (rituximab, omalizumab or ustekinumab) cannot be recommended. (4, C)
- A therapy of AE with mepolizumab may be tried in selected cases unresponsive to standard therapy. (−, D)

Other systemic treatment

Alitretinoin

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

Controlled clinical trial data demonstrating efficacy There is one large, multicenter randomized, placebo-controlled clinical trial involving 1032 patients with chronic hand eczema, about one-third of which are probably atopic hand eczema patients.[87] Improvement of eczema symptoms was seen in 75% of the patients. The response rate of hyperkeratotic hand eczema (49%) and pulpitis sicca type patients (44%) was higher than the dyshidrosiform subtype of hand eczema (33%). The patient group suffering from atopic hand eczema has not been analysed 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 12 weeks in an uncontrolled, open-label trial.[88] Palmar and extrapalmar lesions improved during the trial, as shown by the mTLSS hand eczema score and the SCORAD.

Drug safety profile of alitretinoin As alitretinoin is highly teratogenic, all females of childbearing potential must adhere to a strict birth control programme. Headache is the most frequent clinical side-effect of alitretinoin especially in the first 2 weeks of treatment. Serum lipid and TSH elevation may also occur.

Summary of evidence

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

Alitretinoin is a teratogenic substance. (−)

There are no trial data for its use in children or adolescents. (−)

Recommendations

- Alitretinoin may be used for atopic hand eczema in adult patients of non-childbearing potential unresponsive to topical steroid therapy. (1b, A)
- Alitretinoin might lead to an improvement of both extrapalmar and hand lesions in AE patients. (4, C)

Apremilast

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

QoL,[89] but the drug development programme of apremilast for AE has been stopped.

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

Tofacitinib

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

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

Immunoadsorption

Immunoadsorption (IA) has been used in patients with AE and high serum IgE levels based on the assumption that a reduction in IgE might result in a reduction in disease activity. An investigator initiated open-label pilot study in patients with severe AE recalcitrant to topical and systemic therapy showed that IA resulted in a significant decrease in SCORAD 3 weeks after the first cycle of 5 IA and a further improvement after the second cycle 1 month apart, and in parallel a reduction in skin-bound IgE.[91] A recent study confirmed these results and showed long-term clinical effect of IA in AE patients.[92] Another pilot study in severe AE showed a beneficial effect of immunoadsorption together with subcutaneous application of omalizumab; the serum levels of free IgE and the SCORAD decreased significantly.[93]

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

Mast cell stabilizers

Mast cell stabilizers inhibit mast cell degranulation and thus prevent the release of histamine and other mediators. Oral cromolyn, ketotifen and pemirolast are used for asthma and other allergic diseases, but have not shown any significant effect for the treatment of AE. In the last 5 years, studies investigating these substances in AE have not been published.

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

Leukotriene antagonists

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

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

Intravenous immunoglobulin

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

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

H1R-blocking antihistamines

Traditional histamine 1 receptor (H1R)-blocking antihistamines have been used for decades, in an attempt to relieve pruritus in patients with AE. However, only a few randomized controlled trials have been conducted and they have in the majority shown only a weak or no effect in decreasing pruritus.[99–104] According to a Cochrane search, randomized controlled trials investigating the efficacy of antihistamine monotherapy in AE patients are lacking.[105]

The first generation of sedative antihistamines such as hydroxyzine, clemastine fumarate, doxylamine and dimetindene maleate may allow better pattern in acute situations with exacerbations of AE (evidence level D). Concerning the newer non-sedating antihistamines, studies using loratadine, cetirizine or fexofenadine demonstrated no or only a weak relief of pruritus in AE.[106–108] A significant, but clinically small, antipruritic effect of fexofenadine 60 mg twice daily has been described.[109] An effect on itch of a high dosage of 20–40 mg cetirizine daily has been observed, but this effect was primarily attributed to sedation.[107]

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

In general, antihistamines are safe to use, also for a long period of time,[113] and the major advantage seems to be relief of the symptoms of comorbidities such as allergic asthma, rhinoconjunctivitis, urticarial dermographism and urticaria. Topical antihistamines have no effect on itch beyond that of their cooling vehicles.

H4R-blocking antihistamines

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

Recommendations

- There is not enough evidence to support the general use of both first- and second-generation H1R antihistamines for treatment of pruritus in AE. These may be tried for treatment of pruritus in AE patients, if standard treatment with TCS and emollients is not sufficient. (1b, A)
- Long-term use of sedative antihistamines in childhood may affect sleep quality and is therefore not recommended. (−, D)

Allergen-specific immunotherapy

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

Introduction to allergen-specific immunotherapy for AE

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

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

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

Evidence from controlled clinical trials

Experience in a pair of monozygotic twins with AE (with spring and summer exacerbations) treated either with grass pollen ASIT or placebo in a double-blind fashion showed significant improvement and decrease in serum IgE in the patient treated with ASIT.[121] Several open uncontrolled study designs also demonstrated advantages of ASIT in patients with AE, and these data were often published in national or non-anglosaxon journals. Some investigators in the 1970s and 1980s also showed improvement of AE in controlled trials.[116]

Subcutaneous immunotherapy (SCIT) A double-blind controlled trial of ASIT with *Dermatophagoides pteronyssinus* in children with AE failed to demonstrate superiority over placebo after a standard 8-month course of treatment with tyrosine-

adsorbed house dust mite extracts in 24 house dust mite-allergic children with AE.[122] However, in a second study phase children were randomly allocated to continue with active treatment or placebo for a further 6 months. The placebo effect was high, and the numbers were too small to permit confident conclusions, but the clinical scores suggested that prolonged ASIT may be effective with regard to several objective parameters of AE severity.[122]

A small placebo-controlled study showed AE improvement in 13 of 16 ASIT-treated AE patients, whereas only 4 of 10 placebo-treated AE patients improved.[123] Similar results were reported for AE lesions under ASIT with house dust mite extracts.[124,125] Oral ASIT for *D. pteronyssinus* was not effective in a controlled study enrolling 60 children with AE which were followed for 3 years.[126] Conventional s.c. ASIT ($n = 41$; 76% improved) and sublingual ASIT (SLIT; $n = 48$; 64% improved) showed some efficacy, with adverse drug reactions occurring in 15–20% of both groups.[127] A controlled study applying SLIT with house dust allergens was performed in 56 children with AE aged 5–16 years, but the outcome of this intervention was positive only in patients with mild to moderate AE, but not with severe AE.[128]

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

A large randomized, assessor-blinded clinical trial investigated 89 patients with AE showing a sensitization to house dust mite (CAP-FEIA ≥ 4).[117] Patients were injected weekly with three different doses of HDM allergen extract. With higher allergen doses, a beneficial SCORAD decrease occurred after 8 weeks compared to a control group with an 'active placebo' consisting of very low allergen dose. The effect was maintained over 1 year and was accompanied by lower glucocorticosteroid use.

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

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

A systematic review and meta-analysis of randomized controlled trials published until December 2012 assessed the efficacy of immunotherapy for AE. Eight randomized controlled trials that comprised a total of 385 subjects were analysed. It has been found that ASIT has a significant positive effect on AE patients [odd ratio (OR), 5.35; 95% CI, 1.61–17.77; number needed to treat 3; 95% CI, 2–9]. ASIT showed also significant efficacy in long-term treatment (OR, 6.42; 95% CI, 1.31–7.48) for severe atopic dermatitis (OR, 3.13; 95% CI, 1.31–7.48), and when administered subcutaneously (OR, 4.27; 95% CI, 1.36–13.39). This meta-analysis provides moderate level evidence for the efficacy of SCIT in AE. However, these findings are based on an analysis of a small number of patients, with considerable heterogenicity among trials.[132]

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

Another study analysed 107 patients undergoing SLIT for 12 months. A total of 84 patients finished the trial, compared to the placebo group (53.85%), and the treatment group (77.78%) showed improvement in symptoms.[133]

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

Summary of evidence

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

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

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

Recommendations

- ASIT is currently not recommended as a general treatment option for AE. (2a, B)
- ASIT may be considered for selected patients with house dust mite, birch or grass pollen sensitization, who have severe AE, and a history of clinical exacerbation after exposure to the causative allergen or a positive corresponding atopy patch test. (2a, B)

(a) Treatment recommendation for atopic eczema: adult

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

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

(b) Treatment recommendation for atopic eczema: children

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

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

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

Complementary and alternative medicine in atopic eczema

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

Essential fatty acids

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

Negative results were obtained in a trial on eicosapentaenoic acids from Germany.[149]

A study from Berlin compared the daily administration of 5.4 g docosahexaenoic acid (DHA) in 21 patients who completed the trial with an isoenergetic control of fatty acids ($N = 23$) over 8 weeks. The SCORAD dropped significantly in the DHA group, however, significant differences to control were not observed.[150]

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

A RCT in 20 hospitalized patients with AE comparing infusions of fish oil to soya bean oil revealed marked improvements within 1 week in both groups but a significantly greater effect in those treated with fish oil.[152] Some smaller RCTs have also indicated a beneficial effect,[153–155] although the largest and well reported trial did show a difference between the fish oil and the placebo.[156]

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

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

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

Summary of evidence

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

Recommendations

- Oral application of unsaturated fatty acids is not recommended for treatment of AE. (1a, A)
- Topical application of unsaturated fatty acids as an ingredient in emollients may be tried in selected cases. (D, −)

Phytotherapy

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

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

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

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

Summary of evidence

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

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

Recommendations

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

Chinese herbal medicine (CHM)

Chinese herbs are part of the traditional Chinese medicine which consists of Chinese herbs administered orally or topically, acupuncture, diet and exercise.[171,172] CHM is promoted as treatment for AE, taken orally as decoction, usually consisting of about 10 different herbs. The first positive RCTs of CHM in the treatment of AE outside China were published by Sheehan in 1992.[173] Serious adverse effects including fatal hepatitis have been reported by independent investigators following these trials.[171,174–176] Further trials on Zemaphyte®, a commercial product of Chinese herbs, revealed conflicting results.[177,178]

The oral application of a combination of *Eleutherococcus, Achillea millefolium* and *Lamium album* was not superior to placebo after 2 weeks.[179]

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

Summary of evidence

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

Recommendations

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

Acupuncture/Acupressure

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

Summary of evidence

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

Recommendations

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

Autologous blood therapy

One RCT compared the intramuscular re-injection of 1–3 mL autologous blood over 5 weeks to the injection of the equivalent amount of sterile saline solution.[188] Patients were recruited via press advertisement and finally 30 subjects participated. Over a 9-week period, AE severity measured by SASSAD dropped significantly in the verum group from 23.2 to 10.4 and did not change in the placebo group (21.0–22.5). Significant differences were not observed in health related quality of life and the subjective assessment of pruritus skin appearance and sleep quality. The data suggest a beneficial effect of autologous blood therapy with respect to the signs score. This finding should be confirmed in larger trials and different settings.

Summary of evidence

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

Recommendations

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

Bioresonance

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

Summary of evidence

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

Recommendations

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

Homoeopathy

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

Summary of evidence

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

Recommendations

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

Massage therapy/aroma therapy

The effect of additional massage therapy for AE, applied daily for 20 min over a 1 month period compared to standard therapy alone, was investigated in a randomized trial in 20 children.[195] Greater degrees of improvement in anxiety scores, tactile defensiveness and coping index were reported by parents of children in the active group. Furthermore, clinical signs such as scaling and excoriation improved significantly in the massage group. Appropriate statistical comparisons between groups, however, were not performed. A further small crossover trial in eight children compared massage with essential oils (aroma therapy) to conventional massage.[196] Both treatment groups improved significantly without significant differences between groups. Given the small sample size, conclusions on the beneficial effects of additional aroma therapy cannot be drawn.

Summary of evidence

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

Recommendations

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

Salt baths and thermal spring water balneotherapy

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

Summary of evidence

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

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

Recommendations

- The use of salt baths is not generally recommended for treatment of AE. (4, C)
- Thermal spring water balneotherapy may be considered in mild to moderate AE (B, 2a, 2b)

Vitamins and minerals

A total of six trials were identified investigating vitamins or minerals in the treatment of AE.[206–211] A placebo-controlled study from Italy studied oral vitamin E (400 IU) in 96 patients.[210] Greater clinical improvement was reported for the vitamin E group but without results of statistical tests. Similarly, a smaller study of 49 patients comparing vitamin E plus vitamin B2 to vitamin E or vitamin B2 alone

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

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

Summary of evidence

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

Recommendations

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

Topical vitamin B12 in avocado oil

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

Summary of evidence

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

Recommendations

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

Harms of CAM

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

Psychosomatic counselling

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

Poor adherence to treatment

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

Educational interventions

A Cochrane review analysed ten RCTs of psychological or educational interventions, in addition to conventional therapy, for AE in children.[233] One study of a psychological intervention used biofeedback and hypnotherapy as relaxation techniques vs. discussion only. Three of the four educational

studies identified significant improvements in disease severity in the intervention groups. The fourth trial evaluated long-term outcomes and found a statistically significant improvement ($P < 0.01$) in disease severity and parental quality of life over 12 months in all studied age groups (3 months to 18 years). Heterogeneity in outcome measures and inadequate methodology limited data synthesis in this review. The psychological and educational interventions were delivered by nurses or multidisciplinary teams.[234] Quality of life (QoL) is severely impaired in AE patients,[235] as shown in a recent review: Statistically significant improvements in QoL of AE patients by patient education were reported in five studies, whereas the severity of skin disease improved significantly in three studies of ten studies evaluated. In conclusion, patient education appears to be effective in improving QoL and in reducing the perceived severity of skin disease.[236–238] (See chapter: Educational interventions for AE).

Psychotherapeutic approaches

Most psychological training programmes include relaxation techniques,[239] habit training for social competence and communication as well as coping behaviour and improvement of self-control with regard to disrupting the itch-scratch cycle.

Psychosomatic counselling Randomized controlled trials compared the use of topical corticosteroid alone with steroids together with a behavioural therapy programme which led to a significantly pronounced improvement of skin condition and itch-scratch behaviour.[240]

Behavioural therapy Behavioural therapy against itch was studied, showing a significant improvement in symptoms after 1 year.[241–243] Especially habit reversal techniques improve itch in atopic dermatitis.[244]

Autogenic training Together with cognitive behavioural therapy was studied in a standardized educational programme (see chapter 'Education').[245]

Relaxation Relaxation methods may be more effective in reducing disease severity than discussion only.[246]

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

Summary of evidence

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

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

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

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

Recommendations

- Psychosomatic counselling, psychotherapeutical approaches, behavioural therapy techniques, autogenic training, relaxation techniques, psychological and psychosomatic interventions are recommended in selected patients. (1a, A)
- The indication should be confirmed by specialists in the field of psychodermatology. (−, D)

Educational interventions for atopic eczema

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

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

Educational service delivery models

There are different types of PE programmes running all around the world. These differ in number and certification of the educators, number of participants, age of patients, teaching techniques, duration and frequency of

interventions.[233,250] Thus, because the content of the PE programmes varies greatly, comparison between studies is difficult. For example, while the intervention by Staab[237] entailed 2-h sessions, involving a trained multidisciplinary team, once a week for 6 weeks, the intervention by Shaw *et al.*[251] involved a trained medical student running a single 15-min session. Most of the published intervention programmes are structured as follows:

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

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

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

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

E-health during follow-up of patients with AE

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

Forms of educational intervention tools

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

Summary of evidence

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

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

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

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

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

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

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

Recommendations

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

Conclusion and outlook

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

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

References

1 Ong PY, Ohtake T, Brandt C *et al.* Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med* 2002; **347**: 1151–1160.
2 Weidinger S, Novak N. Atopic dermatitis. *Lancet* 2016; **387**: 1109–1122.
3 Kong HH, Oh J, Deming C *et al.* Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res* 2012; **22**: 850–859.
4 Cornelissen C, Marquardt Y, Czaja K *et al.* IL-31 regulates differentiation and filaggrin expression in human organotypic skin models. *J Allergy Clin Immunol* 2012; **129**: 426–433, 433.e1–8.
5 Schlievert PM, Case LC, Strandberg KL, Abrams BB, Leung DY. Superantigen profile of *Staphylococcus aureus* isolates from patients with steroid-resistant atopic dermatitis. *Clin Infect Dis* 2008; **46**: 1562–1567.
6 Allen HB, Vaze ND, Choi C *et al.* The presence and impact of biofilm-producing staphylococci in atopic dermatitis. *JAMA Dermatol* 2014; **150**: 260–265.
7 Williams MR, Gallo RL. The role of the skin microbiome in atopic dermatitis. *Curr Allergy Asthma Rep* 2015; **15**: 65.
8 Kong HH, Segre JA. Skin microbiome: looking back to move forward. *J Invest Dermatol* 2012; **132**(3 Pt 2): 933–939.
9 Gueniche A, Knaudt B, Schuck E *et al.* Effects of nonpathogenic gram-negative bacterium *Vitreoscilla filiformis* lysate on atopic dermatitis: a prospective, randomized, double-blind, placebo-controlled clinical study. *Br J Dermatol* 2008; **159**: 1357–1363.
10 Bath-Hextall FJ, Birnie AJ, Ravenscroft JC, Williams HC. Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema: an updated Cochrane review. *Br J Dermatol* 2011; **164**: 12–26.
11 Leung TH, Zhang LF, Wang J, Ning S, Knox SJ, Kim SK. Topical hypochlorite ameliorates NF-kappaB-mediated skin diseases in mice. *J Clin Invest* 2013; **123**: 5361–5370.
12 Huang JT, Abrams M, Tlougan B, Rademaker A, Paller AS. Treatment of *Staphylococcus aureus* colonization in atopic dermatitis decreases disease severity. *Pediatrics* 2009; **123**: e808–e814.
13 Matiz C, Tom WL, Eichenfield LF, Pong A, Friedlander SF. Children with atopic dermatitis appear less likely to be infected with community acquired methicillin-resistant *Staphylococcus aureus*: the San Diego experience. *Pediatr Dermatol* 2011; **28**: 6–11.
14 Chiu LS, Chow VC, Ling JM, Hon KL. *Staphylococcus aureus* carriage in the anterior nares of close contacts of patients with atopic dermatitis. *Arch Dermatol* 2010; **146**: 748–752.
15 Gauger A, Mempel M, Schekatz A, Schafer T, Ring J, Abeck D. Silver-coated textiles reduce *Staphylococcus aureus* colonization in patients with atopic eczema. *Dermatology* 2003; **207**: 15–21.
16 Lopes C, Silva D, Delgado L, Correia O, Moreira A. Functional textiles for atopic dermatitis: a systematic review and meta-analysis. *Pediatr Allergy Immunol* 2013; **24**: 603–613.
17 Vlachou C, Thomas KS, Williams HC. A case report and critical appraisal of the literature on the use of DermaSilk in children with atopic dermatitis. *Clin Exp Dermatol* 2009; **34**: e901–e903.
18 Jaeger T, Rothmaier M, Zander H, Ring J, Gutermuth J, Anliker MD. Acid-coated textiles (pH 5.5–6.5) – a new therapeutic strategy for atopic eczema? *Acta Derm Venereol* 2015; **95**: 659–663.
19 Lopes C, Soares J, Tavaria F *et al.* Chitosan coated textiles may improve atopic dermatitis severity by modulating skin staphylococcal profile: a randomized controlled trial. *PLoS One* 2015; **10**: e0142844.
20 Thomas KS, Bradshaw LE, Sach TH *et al.* UK Dermatology Clinical Trials Network's CLOTHES Trial Team. Silk garments plus standard care compared with standard care for treating eczema in children: a randomised, controlled, observer-blind, pragmatic trial (CLOTHES Trial). *PLoS Med* 2017; **14**: e1002280.
21 Wollenberg A, Zoch C, Wetzel S, Plewig G, Przybilla B. Predisposing factors and clinical features of eczema herpeticum: a retrospective analysis of 100 cases. *J Am Acad Dermatol* 2003; **49**: 198–205.
22 Wollenberg A. Eczema herpeticum. *Chem Immunol Allergy* 2012; **96**: 89–95.
23 Ong PY, Leung DY. Bacterial and viral infections in atopic dermatitis: a comprehensive review. *Clin Rev Allergy Immunol* 2016; **51**: 329–337.
24 Wollenberg A, Oranje A, Deleuran M *et al.* ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. *J Eur Acad Dermatol Venereol* 2016; **30**: 729–747.
25 Kreth HW, Hoeger PH, Members of the VZVADsg. Safety, reactogenicity, and immunogenicity of live attenuated varicella vaccine in children between 1 and 9 years of age with atopic dermatitis. *Eur J Pediatr* 2006; **165**: 677–683.
26 Schneider L, Weinberg A, Boguniewicz M *et al.* Immune response to varicella vaccine in children with atopic dermatitis compared with nonatopic controls. *J Allergy Clin Immunol* 2010; **126**: 1306–1307 e2.
27 Osier E, Eichenfield LF. The utility of cantharidin for the treatment of molluscum contagiosum. *Pediatr Dermatol* 2015; **32**: 295.
28 Wollenberg A, Wetzel S, Burgdorf WH, Haas J. Viral infections in atopic dermatitis: pathogenic aspects and clinical management. *J Allergy Clin Immunol* 2003; **112**: 667–674.
29 Rush J, Dinulos JG. Childhood skin and soft tissue infections: new discoveries and guidelines regarding the management of bacterial soft tissue infections, molluscum contagiosum, and warts. *Curr Opin Pediatr* 2016; **28**: 250–257.
30 Wollenberg A, Engler R. Smallpox, vaccination and adverse reactions to smallpox vaccine. *Curr Opin Allergy Clin Immunol* 2004; **4**: 271–275.
31 Reed JL, Scott DE, Bray M. Eczema vaccinatum. *Clin Infect Dis* 2012; **54**: 832–840.
32 Darsow U, Sbornik M, Rombold S *et al.* Long-term safety of replication-defective smallpox vaccine (MVA-BN) in atopic eczema and allergic rhinitis. *J Eur Acad Dermatol Venereol* 2016; **30**: 1971–1977.
33 Neri I, Dondi A, Wollenberg A *et al.* Atypical forms of hand, foot, and mouth disease: a prospective study of 47 Italian children. *Pediatr Dermatol* 2016; **33**: 429–437.
34 Lynch MD, Sears A, Cookson H *et al.* Disseminated coxsackievirus A6 affecting children with atopic dermatitis. *Clin Exp Dermatol* 2015; **40**: 525–528.
35 Johnson VK, Hayman JL, McCarthy CA, Cardona ID. Successful treatment of eczema coxsackium with wet wrap therapy and low-dose topical corticosteroid. *J Allergy Clin Immunol Pract* 2014; **2**: 803–804.
36 Glatz M, Bosshard PP, Hoetzenecker W, Schmid-Grendelmeier P. The role of *Malassezia* spp. in atopic dermatitis. *J Clin Med* 2015; **4**: 1217–1228.
37 Kaffenberger BH, Mathis J, Zirwas MJ. A retrospective descriptive study of oral azole antifungal agents in patients with patch test-negative head and neck predominant atopic dermatitis. *J Am Acad Dermatol* 2014; **71**: 480–483.
38 Svejgaard E, Larsen PO, Deleuran M, Ternowitz T, Roed-Petersen J, Nilsson J. Treatment of head and neck dermatitis comparing itraconazole 200 mg and 400 mg daily for 1 week with placebo. *J Eur Acad Dermatol Venereol* 2004; **18**: 445–449.
39 Brodska P, Panzner P, Pizinger K, Schmid-Grendelmeier P. IgE-mediated sensitization to malassezia in atopic dermatitis: more common in male patients and in head and neck type. *Dermatitis* 2014; **25**: 120–126.
40 Glatz M, Buchner M, von Bartenwerffer W *et al.* Malassezia spp.-specific immunoglobulin E level is a marker for severity of atopic dermatitis in adults. *Acta Derm Venereol* 2015; **95**: 191–196.
41 Schmitt J, Schakel K, Folster-Holst R *et al.* Prednisolone vs. ciclosporin for severe adult eczema. An investigator-initiated double-blind placebo-controlled multicentre trial. *Br J Dermatol* 2010; **162**: 661–668.
42 Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema – a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2007; **21**: 606–619.

43 Czech W, Brautigam M, Weidinger G, Schopf E. A body-weight-independent dosing regimen of cyclosporine microemulsion is effective in severe atopic dermatitis and improves the quality of life. *J Am Acad Dermatol* 2000; **42**: 653–659.
44 van der Schaft J, van Zuilen AD, Deinum J, Bruijnzeel-Koomen CA, de Bruin-Weller MS. Serum creatinine levels during and after long-term treatment with cyclosporin a in patients with severe atopic dermatitis. *Acta Derm Venereol* 2015; **95**: 963–967.
45 van der Schaft J, Politiek K, van den Reek JM *et al.* Drug survival for ciclosporin A in a long-term daily practice cohort of adult patients with atopic dermatitis. *Br J Dermatol* 2015; **172**: 1621–1627.
46 Harper JI, Ahmed I, Barclay G *et al.* Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy. *Br J Dermatol* 2000; **142**: 52–58.
47 Granlund H, Erkko P, Remitz A *et al.* Comparison of cyclosporin and UVAB phototherapy for intermittent one-year treatment of atopic dermatitis. *Acta Derm Venereol* 2001; **81**: 22–27.
48 Zurbriggen B, Wuthrich B, Cachelin AB, Wili PB, Kagi MK. Comparison of two formulations of cyclosporin A in the treatment of severe atopic dermatitis. Aa double-blind, single-centre, cross-over pilot study. *Dermatology* 1999; **198**: 56–60.
49 Berth-Jones J, Takwale A, Tan E *et al.* Azathioprine in severe adult atopic dermatitis: a double-blind, placebo-controlled, crossover trial. *Br J Dermatol* 2002; **147**: 324–330.
50 Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. *Lancet* 2006; **367**: 839–846.
51 Schram ME, Roekevisch E, Leeflang MM, Bos JD, Schmitt J, Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. *J Allergy Clin Immunol* 2011; **128**: 353–359.
52 Caufield M, Tom WL. Oral azathioprine for recalcitrant pediatric atopic dermatitis: clinical response and thiopurine monitoring. *J Am Acad Dermatol* 2013; **68**: 29–35.
53 Murphy LA, Atherton D. A retrospective evaluation of azathioprine in severe childhood atopic eczema, using thiopurine methyltransferase levels to exclude patients at high risk of myelosuppression. *Br J Dermatol* 2002; **147**: 308–315.
54 Hon KL, Ching GK, Leung TF, Chow CM, Lee KK, Ng PC. Efficacy and tolerability at 3 and 6 months following use of azathioprine for recalcitrant atopic dermatitis in children and young adults. *J Dermatolog Treat* 2009; **20**: 141–145.
55 Peyrin-Biroulet L, Khosrotehrani K, Carrat F *et al.* Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology* 2011; **141**: 1621–1628 e1–5.
56 Haeck IM, Knol MJ, Ten Berge O, van Velsen SG, de Bruin-Weller MS, Bruijnzeel-Koomen CA. Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: a randomized controlled trial. *J Am Acad Dermatol* 2011; **64**: 1074–1084.
57 Ballester I, Silvestre JF, Perez-Crespo M, Lucas A. Severe adult atopic dermatitis: treatment with mycophenolate mofetil in 8 patients. *Actas Dermosifiliogr* 2009; **100**: 883–887.
58 Murray ML, Cohen JB. Mycophenolate mofetil therapy for moderate to severe atopic dermatitis. *Clin Exp Dermatol* 2007; **32**: 23–27.
59 Heller M, Shin HT, Orlow SJ, Schaffer JV. Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. *Br J Dermatol* 2007; **157**: 127–132.
60 Waxweiler WT, Agans R, Morrell DS. Systemic treatment of pediatric atopic dermatitis with azathioprine and mycophenolate mofetil. *Pediatr Dermatol* 2011; **28**: 689–694.
61 King RW, Baca MJ, Armenti VT, Kaplan B. Pregnancy outcomes related to mycophenolate exposure in female kidney transplant recipients. *Am J Transplant* 2017; **17**: 151–160.
62 El-Khalawany MA, Hassan H, Shaaban D, Ghonaim N, Eassa B. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: a multicenter experience from Egypt. *Eur J Pediatr* 2013; **172**: 351–356.
63 Weatherhead SC, Wahie S, Reynolds NJ, Meggitt SJ. An open-label, dose-ranging study of methotrexate for moderate-to-severe adult atopic eczema. *Br J Dermatol* 2007; **156**: 346–351.
64 Lyakhovitsky A, Barzilai A, Heyman R *et al.* Low-dose methotrexate treatment for moderate-to-severe atopic dermatitis in adults. *J Eur Acad Dermatol Venereol* 2010; **24**: 43–49.
65 Beck LA, Thaci D, Hamilton JD *et al.* Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med* 2014; **371**: 130–139.
66 Thaci D, Simpson EL, Beck LA *et al.* Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet* 2016; **387**: 40–52.
67 Simpson EL, Bieber T, Guttman-Yassky E *et al.* Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med* 2016; **375**: 2335–2348.
68 Blauvelt A, de Bruin-Weller M, Gooderham M *et al.* Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet* 2017; **389**: 2287–2303.
69 Ruzicka T, Hanifin JM, Furue M *et al.* Anti-interleukin-31 receptor A antibody for atopic dermatitis. *N Engl J Med* 2017; **376**: 826–835.
70 Simon D, Hösli S, Kostylina G, Yawalkar N, Simon HU. Anti-CD20 (rituximab) treatment improves atopic eczema. *J Allergy Clin Immunol* 2008; **121**: 122–128.
71 Sedivá A, Kayserová J, Vernerová E *et al.* Anti-CD20 (rituximab) treatment for atopic eczema. *J Allergy Clin Immunol* 2008; **121**: 1515–1516.
72 Oldhoff JM, Darsow U, Werfel T *et al.* Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. *Allergy* 2005; **60**: 693–696.
73 Oldhoff JM, Darsow U, Werfel T *et al.* No effect of anti-interleukin-5 therapy (mepolizumab) on the atopy patch test in atopic dermatitis patients. *Int Arch Allergy Immunol* 2006; **141**: 290–294.
74 Heil PM, Maurer D, Klein B, Hultsch T, Stingl G. Omalizumab therapy in atopic dermatitis: depletion of IgE does not improve the clinical course – a randomized, placebo-controlled and double blind pilot study. *J Dtsch Dermatol Ges* 2010; **8**: 990–998.
75 Sheinkopf LE, Rafi AW, Do LT, Katz RM, Klaustermeyer WB. Efficacy of omalizumab in the treatment of atopic dermatitis: a pilot study. *Allergy Asthma Proc* 2008; **29**: 530–537.
76 Vigo PG, Girgis KR, Pfuetze BL, Critchlow ME, Fisher J, Hussain I. Efficacy of anti-IgE therapy in patients with atopic dermatitis. *J Am Acad Dermatol* 2006; **55**: 168–170.
77 Incorvaia C, Pravettoni C, Mauro M, Yacoub MR, Tarantini F, Riario-Sforza GG. Effectiveness of omalizumab in a patient with severe asthma and atopic dermatitis. *Monaldi Arch Chest Dis* 2008; **69**: 78–80.
78 Belloni B, Ziai M, Lim A *et al.* Low-dose anti-IgE therapy in patients with atopic eczema with high serum IgE levels. *J Allergy Clin Immunol* 2007; **120**: 1223–1225.
79 Hotze M, Baurecht H, Rodriguez E *et al.* Increased efficacy of omalizumab in atopic dermatitis patients with wild-type filaggrin status and higher serum levels of phosphatidylcholines. *Allergy* 2014; **69**: 132–135.
80 Lacombe Barrios J, Begin P, Paradis L, Hatami A, Paradis J, Des Roches A. Anti-IgE therapy and severe atopic dermatitis: a pediatric perspective. *J Am Acad Dermatol* 2013; **69**: 832–834.
81 Iyengar SR, Hoyte EG, Loza A *et al.* Immunologic effects of omalizumab in children with severe refractory atopic dermatitis: a randomized, placebo-controlled clinical trial. *Int Arch Allergy Immunol* 2013; **162**: 89–93.

82 Doerthe AA, Wang J. Immunologic effects of omalizumab in children with severe refractory atopic dermatitis: a randomized, placebo-controlled clinical trial. *Pediatrics* 2014; **134**: 160.
83 Fernandez-Anton MC, Alfageme Roldan F, Ciudad Blanco C, Suarez Fernandez R. Ustekinumab in the treatment of severe atopic dermatitis: a preliminary report of our experience with 4 patients. *Actas Dermosifiliogr* 2014; **105**: 312–323.
84 Samorano LP, Hanifin JM, Simpson EL, Leshem YA. Inadequate response to ustekinumab in atopic dermatitis - a report of two patients. *J Eur Acad Dermatol Venereol* 2016; **30**: 522–523.
85 Khattri S, Brunner PM, Garcet S *et al.* Efficacy and safety of ustekinumab treatment in adults with moderate-to-severe atopic dermatitis. *Exp Dermatol* 2017; **26**: 28–35.
86 Saeki H, Kabashima K, Tokura Y *et al.* Efficacy and safety of ustekinumab in Japanese patients with severe atopic dermatitis: a randomized, double-blind, placebo-controlled, phase II study. *Br J Dermatol* 2017; **177**: 419–427.
87 Ruzicka T, Lynde CW, Jemec GB *et al.* Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol* 2008; **158**: 808–817.
88 Grahovac M, Molin S, Prinz JC, Ruzicka T, Wollenberg A. Treatment of atopic eczema with oral alitretinoin. *Br J Dermatol* 2010; **162**: 217–218.
89 Samrao A, Berry TM, Goreshi R, Simpson EL. A pilot study of an oral phosphodiesterase inhibitor (apremilast) for atopic dermatitis in adults. *Arch Dermatol* 2012; **148**: 890–897.
90 Levy LL, Urban J, King BA. Treatment of recalcitrant atopic dermatitis with the oral Janus kinase inhibitor tofacitinib citrate. *J Am Acad Dermatol* 2015; **73**: 395–399.
91 Kasperkiewicz M, Schmidt E, Frambach Y *et al.* Improvement of treatment-refractory atopic dermatitis by immunoadsorption: a pilot study. *J Allergy Clin Immunol* 2011; **127**: 267–270.
92 Kasperkiewicz M, Sufke S, Schmidt E, Zillikens D. IgE-specific immunoadsorption for treatment of recalcitrant atopic dermatitis. *JAMA Dermatol* 2014; **150**: 1350–1351.
93 Zink A, Gensbaur A, Zirbs M *et al.* Targeting IgE in severe atopic dermatitis with a combination of immunoadsorption and omalizumab. *Acta Derm Venereol* 2016; **96**: 72–76.
94 Broshtilova V, Gantcheva M. Therapeutic hotline: cysteinyl leukotriene receptor antagonist montelukast in the treatment of atopic dermatitis. *Dermatol Ther* 2010; **23**: 90–93.
95 Holme H, Winckworth LC. Montelukast can reduce the severity and extent of atopic dermatitis. *J Paediatr Child Health* 2013; **49**: 412–415.
96 Roekevisch E, Spuls PI, Kuester D, Limpens J, Schmitt J. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. *J Allergy Clin Immunol* 2014; **133**: 429–438.
97 Jee SJ, Kim JH, Baek HS, Lee HB, Oh JW. Long-term efficacy of intravenous immunoglobulin therapy for moderate to severe childhood atopic dermatitis. *Allergy Asthma Immunol Res* 2011; **3**: 89–95.
98 Paul C, Lahfa M, Bachelez H, Chevret S, Dubertret L. A randomized controlled evaluator-blinded trial of intravenous immunoglobulin in adults with severe atopic dermatitis. *Br J Dermatol* 2002; **147**: 518–522.
99 Doherty V, Sylvester DG, Kennedy CT, Harvey SG, Calthrop JG, Gibson JR. Treatment of itching in atopic eczema with antihistamines with a low sedative profile. *BMJ* 1989; **298**: 96.
100 Henz BM, Metzenauer P, O'Keefe E, Zuberbier T. Differential effects of new-generation H1-receptor antagonists in pruritic dermatoses. *Allergy* 1998; **53**: 180–183.
101 Langeland T, Fagertun HE, Larsen S. Therapeutic effect of loratadine on pruritus in patients with atopic dermatitis. A multi-crossover-designed study. *Allergy* 1994; **49**: 22–26.
102 La Rosa M, Ranno C, Musarra I, Guglielmo F, Corrias A, Bellanti JA. Double-blind study of cetirizine in atopic eczema in children. *Ann Allergy* 1994; **73**: 117–122.
103 Wahlgren CF, Hagermark O, Bergstrom R. The antipruritic effect of a sedative and a non-sedative antihistamine in atopic dermatitis. *Br J Dermatol* 1990; **122**: 545–551.
104 Munday J, Bloomfield R, Goldman M *et al.* Chlorpheniramine is no more effective than placebo in relieving the symptoms of childhood atopic dermatitis with a nocturnal itching and scratching component. *Dermatology* 2002; **205**: 40–45.
105 van Zuuren EJ, Apfelbacher CJ, Fedorowicz Z, Jupiter A, Matterne U, Weisshaar E. No high level evidence to support the use of oral H1 antihistamines as monotherapy for eczema: a summary of a Cochrane systematic review. *Syst Rev* 2014; **3**: 25.
106 Chunharas A, Wisuthsarewong W, Wananukul S, Viravan S. Therapeutic efficacy and safety of loratadine syrup in childhood atopic dermatitis treated with mometasone furoate 0.1 per cent cream. *J Med Assoc Thai* 2002; **85**: 482–487.
107 Hannuksela M, Kalimo K, Lammintausta K *et al.* Dose ranging study: cetirizine in the treatment of atopic dermatitis in adults. *Ann Allergy* 1993; **70**: 127–133.
108 Kawakami T, Kaminishi K, Soma Y, Kushimoto T, Mizoguchi M. Oral antihistamine therapy influences plasma tryptase levels in adult atopic dermatitis. *J Dermatol Sci* 2006; **43**: 127–134.
109 Kawashima M, Tango T, Noguchi T, Inagi M, Nakagawa H, Harada S. Addition of fexofenadine to a topical corticosteroid reduces the pruritus associated with atopic dermatitis in a 1-week randomized, multicentre, double-blind, placebo-controlled, parallel-group study. *Br J Dermatol* 2003; **148**: 1212–1221.
110 Diepgen TL, Early Treatment of the Atopic Child Study G. Long-term treatment with cetirizine of infants with atopic dermatitis: a multi-country, double-blind, randomized, placebo-controlled trial (the ETAC trial) over 18 months. *Pediatr Allergy Immunol* 2002; **13**: 278–286.
111 Yamanaka K, Motomura E, Noro Y *et al.* Olopatadine, a non-sedating H1 antihistamine, decreases the nocturnal scratching without affecting sleep quality in atopic dermatitis. *Exp Dermatol* 2015; **24**: 227–229.
112 Church MK, Maurer M. H1 – antihistamines and itch in atopic dermatitis. *Exp Dermatol* 2015; **24**: 332–333.
113 Simons FE, Early Prevention of Asthma in Atopic Children Study G. Safety of levocetirizine treatment in young atopic children: an 18-month study. *Pediatr Allergy Immunol* 2007; **18**: 535–542.
114 Thurmond RL. The histamine H4 receptor: from orphan to the clinic. *Front Pharmacol* 2015; **6**: 65.
115 Bussmann C, Bockenhoff A, Henke H, Werfel T, Novak N. Does allergen-specific immunotherapy represent a therapeutic option for patients with atopic dermatitis? *J Allergy Clin Immunol* 2006; **118**: 1292–1298.
116 Darsow U, Forer I, Ring J. Allergen-specific immunotherapy in atopic eczema. *Curr Allergy Asthma Rep* 2011; **11**: 277–283.
117 Werfel T, Breuer K, Rueff F *et al.* Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multi-centre, randomized, dose-response study. *Allergy* 2006; **61**: 202–205.
118 Darsow U, Behrendt H, Ring J. Gramineae pollen as trigger factors of atopic eczema: evaluation of diagnostic measures using the atopy patch test. *Br J Dermatol* 1997; **137**: 201–207.
119 Darsow U, Vieluf D, Ring J. Evaluating the relevance of aeroallergen sensitization in atopic eczema with the atopy patch test: a randomized, double-blind multicenter study. Atopy Patch Test Study Group. *J Am Acad Dermatol* 1999; **40**(2 Pt 1): 187–193.
120 Tan BB, Weald D, Strickland I, Friedmann PS. Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. *Lancet* 1996; **347**: 15–18.
121 Ring J. Successful hyposensitization treatment in atopic eczema: results of a trial in monozygotic twins. *Br J Dermatol* 1982; **107**: 597–602.
122 Glover MT, Atherton DJ. A double-blind controlled trial of hyposensitization to *Dermatophagoides pteronyssinus* in children with atopic eczema. *Clin Exp Allergy* 1992; **22**: 440–446.

123 Kaufman HS, Roth HL. Hyposensitization with alum precipitated extracts in atopic dermatitis: a placebo-controlled study. *Ann Allergy* 1974; **32**: 321–330.
124 Warner JO, Price JF, Soothill JF, Hey EN. Controlled trial of hyposensitisation to *Dermatophagoides pteronyssinus* in children with asthma. *Lancet* 1978; **2**: 912–915.
125 Zachariae H, Cramers M, Herlin T *et al.* Non-specific immunotherapy and specific hyposensitization in severe atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1985; **114**: 48–54.
126 Galli E, Chini L, Nardi S *et al.* Use of a specific oral hyposensitization therapy to *Dermatophagoides pteronyssinus* in children with atopic dermatitis. *Allergol Immunopathol (Madr)* 1994; **22**: 18–22.
127 Mosca M, Albani-Rocchetti G, Vignini MA, Ubezio S, Nume AG, Di Silverio A. La vaccinoterapia sub-linguale nella dermatite atopica. *Ital Dermatol Venereol* 1993; **128**: 79–83.
128 Pajno GB, Caminiti L, Vita D *et al.* Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized, double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2007; **120**: 164–170.
129 Noh G, Lee KY. Pilot study of IFN-gamma-induced specific hyposensitization for house dust mites in atopic dermatitis: IFN-gamma-induced immune deviation as a new therapeutic concept for atopic dermatitis. *Cytokine* 2000; **12**: 472–476.
130 Silny W, Czarnecka-Operacz M. Spezifische Immuntherapie bei der Behandlung von Patienten mit atopischer Dermatitis. Ergebnisse einer placebokontrollierten Doppelblindstudie. *Allergologie* 2006; **29**: 171–183.
131 Novak N, Bieber T, Hoffmann M *et al.* Efficacy and safety of subcutaneous allergen-specific immunotherapy with depigmented polymerized mite extract in atopic dermatitis. *J Allergy Clin Immunol* 2012; **130**: 925–931 e4.
132 Bae JM, Choi YY, Park CO, Chung KY, Lee KH. Efficacy of allergen-specific immunotherapy for atopic dermatitis: a systematic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol* 2013; **132**: 110–117.
133 Qin YE, Mao JR, Sang YC, Li WX. Clinical efficacy and compliance of sublingual immunotherapy with Dermatophagoides farinae drops in patients with atopic dermatitis. *Int J Dermatol* 2014; **53**: 650–655.
134 Liu L, Guo D, Liang Q *et al.* The efficacy of sublingual immunotherapy with *Dermatophagoides farinae* vaccine in a murine atopic dermatitis model. *Clin Exp Allergy* 2015; **45**: 815–822.
135 Artik S, Ruzicka T. Complementary therapy for atopic eczema and other allergic skin diseases. *Dermatol Ther* 2003; **16**: 150–163.
136 Ernst E, Resch K, Mills S. Complementary medicine – a definition. *Br J Gen Pract* 1995; **45**: 506.
137 Happle R. The essence of alternative medicine. A dermatologist's view from Germany. *Arch Dermatol* 1998; **134**: 1455–1460.
138 Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000; **4**: 1–191.
139 Morse PF, Horrobin DF, Manku MS *et al.* Meta-analysis of placebo-controlled studies of the efficacy of Epogam in the treatment of atopic eczema. Relationship between plasma essential fatty acid changes and clinical response. *Br J Dermatol* 1989; **121**: 75–90.
140 Bamford JT, Gibson RW, Renier CM. Atopic eczema unresponsive to evening primrose oil (linoleic and gamma-linolenic acids). *J Am Acad Dermatol* 1985; **13**: 959–965.
141 Nankervis H, Thomas KS, Delamere FM, Barbarot S, Rogers NK, Williams HC. Scoping Systematic Review of Treatments for Eczema. NIHR Journals Library, Southampton, UK: 2016.
142 Bahmer FA, Schafer J. Treatment of atopic dermatitis with borage seed oil (Glandol)–a time series analytic study. *Kinderarztl Prax* 1992; **60**: 199–202.
143 Borrek S, Hildebrandt A, Forster J. Gamma-linolenic-acid-rich borage seed oil capsules in children with atopic dermatitis. A placebo-controlled double-blind study. *Klin Padiatr* 1997; **209**: 100–104.
144 Buslau M, Thaci D. Atopic dermatitis: borage oil for systemic therapy. *Z Dermatol* 1996; **182**: 131–132.
145 Valsecchi R, Di Landro A, Pansera B, Reseghetti A. Gammalinolenic acid in the treatment of atopic dermatitis. *J Eur Acad Dermatol Venereol* 1996; **7**: 77–79.
146 Henz BM, Jablonska S, van de Kerkhof PC *et al.* Double-blind, multicentre analysis of the efficacy of borage oil in patients with atopic eczema. *Br J Dermatol* 1999; **140**: 685–688.
147 Takwale A, Tan E, Agarwal S *et al.* Efficacy and tolerability of borage oil in adults and children with atopic eczema: randomised, double blind, placebo controlled, parallel group trial. *BMJ* 2003; **327**: 1385.
148 Senapati S, Banerjee S, Gangopadhyay DN. Evening primrose oil is effective in atopic dermatitis: a randomized placebo-controlled trial. *Indian J Dermatol Venereol Leprol* 2008; **74**: 447–452.
149 Ring J, Kunz B. Unsaturated fatty acids in the treatment of atopic eczema. In: Ruzicka T, Ring J, Przybilla B, eds. Handbook of Atopic Eczema. Springer, Berlin, 1991: 429–434.
150 Koch C, Dolle S, Metzger M *et al.* Docosahexaenoic acid (DHA) supplementation in atopic eczema: a randomized, double-blind, controlled trial. *Br J Dermatol* 2008; **158**: 786–792.
151 Callaway J, Schwab U, Harvima I *et al.* Efficacy of dietary hempseed oil in patients with atopic dermatitis. *J Dermatolog Treat* 2005; **16**: 87–94.
152 Mayser P, Mayer K, Mahloudjian M *et al.* A double-blind, randomized, placebo-controlled trial of n-3 versus n-6 fatty acid-based lipid infusion in atopic dermatitis. *JPEN J Parenter Enteral Nutr* 2002; **26**: 151–158.
153 Bjorneboe A, Soyland E, Bjorneboe GE, Rajka G, Drevon CA. Effect of dietary supplementation with eicosapentaenoic acid in the treatment of atopic dermatitis. *Br J Dermatol* 1987; **117**: 463–469.
154 Bjorneboe A, Soyland E, Bjorneboe GE, Rajka G, Drevon CA. Effect of n-3 fatty acid supplement to patients with atopic dermatitis. *J Intern Med Suppl* 1989; **731**: 233–236.
155 Gimenez-Arnau A, Barranco C, Alberola M *et al.* Effects of linoleic acid supplements on atopic dermatitis. *Adv Exp Med Biol* 1997; **433**: 285–289.
156 Soyland E, Funk J, Rajka G *et al.* Dietary supplementation with very long-chain n-3 fatty acids in patients with atopic dermatitis. A double-blind, multicentre study. *Br J Dermatol* 1994; **130**: 757–764.
157 Anstey A, Quigley M, Wilkinson J. Topical evening primrose oil as treatment for atopic eczema. *J Dermatol Treat* 1990; **1**: 199–201.
158 Ferreira M, Fiadeiro T, Silva M, Soares A. Topical gamma-linolenic acid therapy in atopic dermatitis. A clinical and biometric evaluation. *Allergo J* 1998; **7**: 213–216.
159 Gehring W, Bopp R, Rippke F, Gloor M. Effect of topically applied evening primrose oil on epidermal barrier function in atopic dermatitis as a function of vehicle. *Arzneimittelforschung* 1999; **49**: 635–642.
160 Goebel AS, Knie U, Abels C, Wohlrab J, Neubert RH. Dermal targeting using colloidal carrier systems with linoleic acid. *Eur J Pharm Biopharm* 2010; **75**: 162–172.
161 Bamford JT, Ray S, Musekiwa A, van Gool C, Humphreys R, Ernst E. Oral evening primrose oil and borage oil for eczema. *Cochrane Database Syst Rev* 2013; (4): CD004416.
162 Bedi MK, Shenefelt PD. Herbal therapy in dermatology. *Arch Dermatol* 2002; **138**: 232–242.
163 Patzelt-Wenczler R, Ponce-Poschl E. Proof of efficacy of Kamillosan(R) cream in atopic eczema. *Eur J Med Res* 2000; **5**: 171–175.
164 Schempp CM, Hezel S, Simon JC. Topical treatment of atopic dermatitis with Hypericum cream. A randomised, placebo-controlled, double-blind half-side comparison study. *Hautarzt* 2003; **54**: 248–253.
165 Klovekorn W, Tepe A, Danesch U. A randomized, double-blind, vehicle-controlled, half-side comparison with a herbal ointment containing *Mahonia aquifolium*, *Viola tricolor* and *Centella asiatica* for the treatment of mild-to-moderate atopic dermatitis. *Int J Clin Pharmacol Ther* 2007; **45**: 583–591.
166 Ernst E. Adverse effects of herbal drugs in dermatology. *Br J Dermatol* 2000; **143**: 923–929.
167 Giordano-Labadie F, Schwarze HP, Bazex J. Allergic contact dermatitis from camomile used in phytotherapy. *Contact Dermatitis* 2000; **42**: 247.

168 Bircher AJ, Niederer M, Hohl C, Surber C. Stealth triamcinolone acetonide in a phytocosmetic cream. *Br J Dermatol* 2002; **146**: 531–532.
169 Mandeau A, Aries MF, Boe JF *et al.* Rhealba(R) oat plantlet extract: evidence of protein-free content and assessment of regulatory activity on immune inflammatory mediators. *Planta Med* 2011; **77**: 900–906.
170 Stalder JF, Tennstedt D, Deleuran M *et al.* Fragility of epidermis and its consequence in dermatology. *J Eur Acad Dermatol Venereol* 2014; **28**(4): 1–18.
171 Koo J, Arain S. Traditional Chinese medicine for the treatment of dermatologic disorders. *Arch Dermatol* 1998; **134**: 1388–1393.
172 Vender RB. Alternative treatments for atopic dermatitis: a selected review. *Skin Therapy Lett* 2002; **7**: 1–5.
173 Sheehan MP, Rustin MH, Atherton DJ *et al.* Efficacy of traditional Chinese herbal therapy in adult atopic dermatitis. *Lancet* 1992; **340**: 13–17.
174 Mostefa-Kara N, Pauwels A, Pines E, Biour M, Levy VG. Fatal hepatitis after herbal tea. *Lancet* 1992; **340**: 674.
175 Wang L, Lu L. Analysis of 162 reported cases of side effects of Chinese medical material. *J Beijing Clin Pharm* 1992; **5**: 50–55.
176 Perharic L, Shaw D, Leon C, De Smet PA, Murray VS. Possible association of liver damage with the use of Chinese herbal medicine for skin disease. *Vet Hum Toxicol* 1995; **37**: 562–566.
177 Latchman Y, Banerjee P, Poulter LW, Rustin M, Brostoff J. Association of immunological changes with clinical efficacy in atopic eczema patients treated with traditional Chinese herbal therapy (Zemaphyte). *Int Arch Allergy Immunol* 1996; **109**: 243–249.
178 Fung AY, Look PC, Chong LY, But PP, Wong E. A controlled trial of traditional Chinese herbal medicine in Chinese patients with recalcitrant atopic dermatitis. *Int J Dermatol* 1999; **38**: 387–392.
179 Shapira MY, Raphaelovich Y, Gilad L, Or R, Dumb AJ, Ingber A. Treatment of atopic dermatitis with herbal combination of *Eleutherococcus*, *Achillea millefolium*, and *Lamium album* has no advantage over placebo: a double blind, placebo-controlled, randomized trial. *J Am Acad Dermatol* 2005; **52**: 691–693.
180 Gu S, Yang AW, Xue CC *et al.* Chinese herbal medicine for atopic eczema. *Cochrane Database Syst Rev* 2013; (9): CD008642.
181 Tan HY, Zhang AL, Chen D, Xue CC, Lenon GB. Chinese herbal medicine for atopic dermatitis: a systematic review. *J Am Acad Dermatol* 2013; **69**: 295–304.
182 Liu J, Mo X, Wu D *et al.* Efficacy of a Chinese herbal medicine for the treatment of atopic dermatitis: a randomised controlled study. *Complement Ther Med* 2015; **23**: 644–651.
183 Chung-Jen C, Hsin-Su Y. Acupuncture, electrostimulation, and reflex therapy in dermatology. *Dermatol Ther* 2003; **16**: 87–92.
184 Adaskevich VP. Clinical efficacy and immunoregulatory and neurohumoral effects of MM therapy in patients with atopic dermatitis. *Crit Rev Biomed Eng* 2000; **28**: 11–21.
185 Pfab F, Huss-Marp J, Gatti A *et al.* Influence of acupuncture on type I hypersensitivity itch and the wheal and flare response in adults with atopic eczema – a blinded, randomized, placebo-controlled, crossover trial. *Allergy* 2010; **65**: 903–910.
186 Pfab F, Kirchner MT, Huss-Marp J *et al.* Acupuncture compared with oral antihistamine for type I hypersensitivity itch and skin response in adults with atopic dermatitis: a patient- and examiner-blinded, randomized, placebo-controlled, crossover trial. *Allergy* 2012; **67**: 566–573.
187 Lee KC, Keyes A, Hensley JR *et al.* Effectiveness of acupressure on pruritus and lichenification associated with atopic dermatitis: a pilot trial. *Acupunct Med* 2012; **30**: 8–11.
188 Pittler MH, Armstrong NC, Cox A, Collier PM, Hart A, Ernst E. Randomized, double-blind, placebo-controlled trial of autologous blood therapy for atopic dermatitis. *Br J Dermatol* 2003; **148**: 307–313.
189 Schoni MH, Nikolaizik WH, Schoni-Affolter F. Efficacy trial of bioresonance in children with atopic dermatitis. *Int Arch Allergy Immunol* 1997; **112**: 238–246.
190 Ernst E. The usage of complementary therapies by dermatological patients: a systematic review. *Br J Dermatol* 2000; **142**: 857–861.
191 Eichler R, Frank H. Die Homöopathische Behandlung der Neurodermitis bei Kindern und Jugendlichen. Haug, Stuttgart, 2002.
192 Itamura R, Hosoya R. Homeopathic treatment of Japanese patients with intractable atopic dermatitis. *Homeopathy* 2003; **92**: 108–114.
193 Remy W, Rakoski J, Siebenwirth J, Ulm K, Wiesenauer M. Classical homoeopathic treatment in atopic dermatitis. Study protocol. *Allergologie* 1995; **18**: 246–252.
194 Siebenwirth J, Lüdtke R, Remy W, Rakoski J, Borelli S, Ring J. Wirksamkeit von klassisch-homöopathischer Therapie bei atopischem Ekzem. *Forsch Komplementmed* 2009; **16**: 315–323.
195 Schachner L, Field T, Hernandez-Reif M, Duarte AM, Krasnegor J. Atopic dermatitis symptoms decreased in children following massage therapy. *Pediatr Dermatol* 1998; **15**: 390–395.
196 Anderson C, Lis-Balchin M, Kirk-Smith M. Evaluation of massage with essential oils on childhood atopic eczema. *Phytother Res* 2000; **14**: 452–456.
197 Halevy S, Sukenik S. Different modalities of spa therapy for skin diseases at the Dead Sea area. *Arch Dermatol* 1998; **134**: 1416–1420.
198 Harari M, Shani J, Seidl V, Hristakieva E. Climatotherapy of atopic dermatitis at the Dead Sea: demographic evaluation and cost-effectiveness. *Int J Dermatol* 2000; **39**: 59–69.
199 Shani J, Seidl V, Hristakieva E, Stanimirovic A, Burdo A, Harari M. Indications, contraindications and possible side-effects of climatotherapy at the Dead-Sea. *Int J Dermatol* 1997; **36**: 481–492.
200 Giryes H, Friger M, Sarov B. Treatment of atopic dermatitis in the Dead Sea area: biology and therapy of inflammatory skin diseases. International Symposium at the Dead Sea Dead Sea Israel. 1997.
201 Schiffner R, Schiffner-Rohe J, Gerstenhauer M, Landthaler M, Hofstadter F, Stolz W. Dead Sea treatment – principle for outpatient use in atopic dermatitis: safety and efficacy of synchronous balneophototherapy using narrowband UVB and bathing in Dead Sea salt solution. *Eur J Dermatol* 2002; **12**: 543–548.
202 Dittmar HC, Pflieger D, Schempp CM, Schopf E, Simon JC. Comparison of balneophototherapy and UVA/B mono-phototherapy in patients with subacute atopic dermatitis. *Hautarzt* 1999; **50**: 649–653.
203 Zimmermann J, Utermann S. Photo-brine therapy in patients with psoriasis and neurodermatitis atopica. *Hautarzt* 1994; **45**: 849–853.
204 Adachi J, Sumitsuzi H, Endo K, Fukuzumi T, Aoki T. Evaluation of the effect of short-term application of deep sea water on atopic dermatitis. *Arerugi* 1998; **47**: 57–60.
205 Farina S, Gisondi P, Zanoni M *et al.* Balneotherapy for atopic dermatitis in children at Comano spa in Trentino, Italy. *J Dermatolog Treat* 2011; **22**: 366–371.
206 Czeizel AE, Dobo M. Postnatal somatic and mental development after periconceptional multivitamin supplementation. *Arch Dis Child* 1994; **70**: 229–233.
207 Fairris GM, Perkins PJ, Lloyd B, Hinks L, Clayton BE. The effect on atopic dermatitis of supplementation with selenium and vitamin E. *Acta Derm Venereol* 1989; **69**: 359–362.
208 Hakagawa R, Ogino Y. Effects of combination therapy with vitamins E and B2 on skin diseases. Double blind controlled clinical trial. *Skin Res* 1989; **31**: 856–881.
209 Mabin DC, Hollis S, Lockwood J, David TJ. Pyridoxine in atopic dermatitis. *Br J Dermatol* 1995; **133**: 764–767.
210 Tsoureli-Nikita E, Hercogova J, Lotti T, Menchini G. Evaluation of dietary intake of vitamin E in the treatment of atopic dermatitis: a study of the clinical course and evaluation of the immunoglobulin E serum levels. *Int J Dermatol* 2002; **41**: 146–150.
211 Sidbury R, Sullivan AF, Thadhani RI, Camargo CA Jr. Randomized controlled trial of vitamin D supplementation for winter-related atopic dermatitis in Boston: a pilot study. *Br J Dermatol* 2008; **159**: 245–247.
212 Ewing CI, Gibbs AC, Ashcroft C, David TJ. Failure of oral zinc supplementation in atopic eczema. *Eur J Clin Nutr* 1991; **45**: 507–510.
213 Udompataikul M, Huajai S, Chalermchai T, Taweechotipatr M, Kamanamool N. The effects of oral vitamin D supplement on atopic

dermatitis: a clinical trial with *Staphylococcus aureus* colonization determination. *J Med Assoc Thai* 2015; **98**(9): S23–S30.
214 Amestejani M, Salehi BS, Vasigh M *et al.* Vitamin D supplementation in the treatment of atopic dermatitis: a clinical trial study. *J Drugs Dermatol* 2012; **11**: 327–330.
215 Camargo CA Jr, Ganmaa D, Sidbury R, Erdenedelger K, Radnaakhand N, Khandsuren B. Randomized trial of vitamin D supplementation for winter-related atopic dermatitis in children. *J Allergy Clin Immunol* 2014; **134**: 831–835 e1.
216 Hata TR, Audish D, Kotol P *et al.* A randomized controlled double-blind investigation of the effects of vitamin D dietary supplementation in subjects with atopic dermatitis. *J Eur Acad Dermatol Venereol* 2014; **28**: 781–789.
217 Norizoe C, Akiyama N, Segawa T *et al.* Increased food allergy and vitamin D: randomized, double-blind, placebo-controlled trial. *Pediatr Int* 2014; **56**: 6–12.
218 Javanbakht MH, Keshavarz SA, Djalali M *et al.* Randomized controlled trial using vitamins E and D supplementation in atopic dermatitis. *J Dermatolog Treat* 2011; **22**: 144–150.
219 Stucker M, Pieck C, Stoerb C, Niedner R, Hartung J, Altmeyer P. Topical vitamin B12–a new therapeutic approach in atopic dermatitis-evaluation of efficacy and tolerability in a randomized placebo-controlled multicentre clinical trial. *Br J Dermatol* 2004; **150**: 977–983.
220 Januchowski R. Evaluation of topical vitamin B(12) for the treatment of childhood eczema. *J Altern Complement Med* 2009; **15**: 387–389.
221 Feldman SR, Vrijens B, Gieler U, Piaserico S, Puig L, van de Kerkhof P. Treatment adherence interventions studies in dermatology and guidance on how to support adherence. *Am J Clin Dermatol* 2017; **18**: 253–271.
222 Arkwright PD, Motala C, Subramanian H *et al.* Management of difficult-to-treat atopic dermatitis. *J Allergy Clin Immunol Pract* 2013; **1**: 142–151.
223 Bass AM, Anderson KL, Feldman SR. Interventions to increase treatment adherence in pediatric atopic dermatitis: a systematic review. *J Clin Med* 2015; **4**: 231–242.
224 Kupfer J, Gieler U, Braun A, Niemeier V, Huzler C, Renz H. Stress and atopic eczema. *Int Arch Allergy Immunol* 2001; **124**: 354–355.
225 Chang HY, Suh DI, Yang SI *et al.* Prenatal maternal distress affects atopic dermatitis in offspring mediated by oxidative stress. *J Allergy Clin Immunol* 2016; **138**: 468–475.
226 Peters EM, Michenko A, Kupfer J *et al.* Mental stress in atopic dermatitis – neuronal plasticity and the cholinergic system are affected in atopic dermatitis and in response to acute experimental mental stress in a randomized controlled pilot study. *PLoS One* 2014; **9**: e113552.
227 Raap U, Werfel T, Jaeger B, Schmid-Ott G. Atopic dermatitis and psychological stress. *Hautarzt* 2003; **54**: 925–929.
228 Gieler U. Psychosomatic and psychobiological aspects of atopic eczema. In: Ring J, Przybilla B, Ruzicka T, eds. Handbook of Atopic Eczema. Springer, Berlin, 2006: 544–556.
229 Koblenzer CS, Koblenzer PJ. Chronic intractable atopic eczema. Its occurrence as a physical sign of impaired parent-child relationships and psychologic developmental arrest: improvement through parent insight and education. *Arch Dermatol* 1988; **124**: 1673–1677.
230 Dalgard FJ, Gieler U, Tomas-Aragones L *et al.* The psychosocial burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. *J Invest Dermatol* 2015; **135**: 984–991.
231 Gieler U, Effendy I. Psychosomatische aspekte in der dermatologie. *Aktuelle Derm* 1984; **10**: 103–160.
232 Ring J, Palos E, Zimmermann F. Psychosomatic aspects of parent-child relations in atopic eczema in childhood. I. Psychodiagnostic test procedures in parents and children in comparison with somatic findings. *Hautarzt* 1986; **37**: 560–567.
233 Ersser SJ, Cowdell F, Latter S *et al.* Psychological and educational interventions for atopic eczema in children. *Cochrane Database Syst Rev* 2014; (1): CD004054.
234 Norris S, Ortiz DD, Sullo E. FPIN's clinical inquiries. Complementary and alternative therapies for atopic dermatitis. *Am Fam Physician* 2012; **85**: 817–823.
235 Finlay AY. Measurement of disease activity and outcome in atopic dermatitis. *Br J Dermatol* 1996; **135**: 509–515.
236 de Bes J, Legierse CM, Prinsen CA, de Korte J. Patient education in chronic skin diseases: a systematic review. *Acta Derm Venereol* 2011; **91**: 12–17.
237 Staab D, Diepgen TL, Fartasch M *et al.* Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: multicentre, randomised controlled trial. *BMJ* 2006; **332**: 933–938.
238 Heratizadeh A, Werfel T, Wollenberg A *et al.* Effects of structured patient education in adult atopic dermatitis – multi-center randomized controlled trial. *J Allergy Clin Immunol* 2017; **140**: 845–853.
239 Bae BG, Oh SH, Park CO *et al.* Progressive muscle relaxation therapy for atopic dermatitis: objective assessment of efficacy. *Acta Derm Venereol* 2012; **92**: 57–61.
240 Noren P, Melin L. The effect of combined topical steroids and habit-reversal treatment in patients with atopic dermatitis. *Br J Dermatol* 1989; **121**: 359–366.
241 Evers AW, Duller P, de Jong EM *et al.* Effectiveness of a multidisciplinary itch-coping training programme in adults with atopic dermatitis. *Acta Derm Venereol* 2009; **89**: 57–63.
242 Schut C, Mollanazar NK, Kupfer J, Gieler U, Yosipovitch G. Psychological interventions in the treatment of chronic itch. *Acta Derm Venereol* 2016; **96**: 157–161.
243 Niebel G, ed. Behavioral Medicine of Chronic Dermatological Disorders – Interdisciplinary Perspectives on Atopic Dermatitis and Its Treatment. Huber, Bern, 1990.
244 Daunton A, Bridgett C, Goulding JM. Habit reversal for refractory atopic dermatitis: a review. *Br J Dermatol* 2016; **174**: 657–659.
245 Ehlers A, Stangier U, Gieler U. Treatment of atopic dermatitis: a comparison of psychological and dermatological approaches to relapse prevention. *J Consult Clin Psychol* 1995; **63**: 624–635.
246 Farasat H. Cochrane review update: psychological and educational interventions for atopic eczema in children. *Community Pract* 2014; **87**: 11–12.
247 Breuer K, Matterne U, Diepgen TL *et al.* Predictors of benefit from an atopic dermatitis education programme. *Pediatr Allergy Immunol* 2014; **25**: 489–495.
248 Batchelor JM, Ridd MJ, Clarke T *et al.* The Eczema Priority Setting Partnership: a collaboration between patients, carers, clinicians and researchers to identify and prioritize important research questions for the treatment of eczema. *Br J Dermatol* 2013; **168**: 577–582.
249 Barbarot S, Bernier C, Deleuran M *et al.* Therapeutic patient education in children with atopic dermatitis: position paper on objectives and recommendations. *Pediatr Dermatol* 2013; **30**: 199–206.
250 Stalder JF, Bernier C, Ball A *et al.* Therapeutic patient education in atopic dermatitis: worldwide experiences. *Pediatr Dermatol* 2013; **30**: 329–334.
251 Shaw M, Morrell DS, Goldsmith LA. A study of targeted enhanced patient care for pediatric atopic dermatitis (STEP PAD). *Pediatr Dermatol* 2008; **25**: 19–24.
252 Grillo M, Gassner L, Marshman G, Dunn S, Hudson P. Pediatric atopic eczema: the impact of an educational intervention. *Pediatr Dermatol* 2006; **23**: 428–436.
253 Weisshaar E, Diepgen TL, Bruckner T *et al.* Itch intensity evaluated in the German Atopic Dermatitis Intervention Study (GADIS): correlations with quality of life, coping behaviour and SCORAD severity in 823 children. *Acta Derm Venereol* 2008; **88**: 234–239.
254 Kupfer J, Gieler U, Diepgen TL *et al.* Structured education program improves the coping with atopic dermatitis in children and their parents-a multicenter, randomized controlled trial. *J Psychosom Res* 2010; **68**: 353–358.

255 Pustišek N, Šitum M, Vurnek Živković M, Ljubojević Hadžavdić S, Vurnek M, Niseteo T. The significance of structured parental educational intervention on childhood atopic dermatitis: a randomized controlled trial. *J Eur Acad Dermatol Venereol* 2016; **30**: 806–812.
256 Moore EJ, Williams A, Manias E, Varigos G, Donath S. Eczema workshops reduce severity of childhood atopic eczema. *Australas J Dermatol* 2009; **50**: 100–106.
257 Darsow U, Wollenberg A, Simon D *et al.* ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. *J Eur Acad Dermatol Venereol* 2010; **24**: 317–328.
258 Courtenay M, Carey N. A review of the impact and effectiveness of nurse-led care in dermatology. *J Clin Nurs* 2007; **16**: 122–128.
259 Schuttelaar ML, Vermeulen KM, Drukker N, Coenraads PJ. A randomized controlled trial in children with eczema: nurse practitioner vs. dermatologist. *Br J Dermatol* 2010; **162**: 162–170.
260 Foster G, Taylor SJ, Eldridge SE, Ramsay J, Griffiths CJ. Self-management education programmes by lay leaders for people with chronic conditions. *Cochrane Database Syst Rev* 2007; (4): CD005108.
261 Cork MJ, Britton J, Butler L, Young S, Murphy R, Keohane SG. Comparison of parent knowledge, therapy utilization and severity of atopic eczema before and after explanation and demonstration of topical therapies by a specialist dermatology nurse. *Br J Dermatol* 2003; **149**: 582–589.
262 Laurant M, Reeves D, Hermens R *et al.* Substitution of doctors by nurses in primary care. *Cochrane Database Syst Rev* 2005; (2): CD001271.
263 van Os-Medendorp H, Koffijberg H, Eland-de Kok PC *et al.* E-health in caring for patients with atopic dermatitis: a randomized controlled cost-effectiveness study of internet-guided monitoring and online self-management training. *Br J Dermatol* 2012; **166**: 1060–1068.
264 Armstrong AW, Kim RH, Idriss NZ, Larsen LN, Lio PA. Online video improves clinical outcomes in adults with atopic dermatitis: a randomized controlled trial. *J Am Acad Dermatol* 2011; **64**: 502–507.
265 Ulff E, Maroti M, Serup J. Fluorescent cream used as an educational intervention to improve the effectiveness of self-application by patients with atopic dermatitis. *J Dermatolog Treat* 2013; **24**: 268–271.
266 Shi VY, Nanda S, Lee K, Armstrong AW, Lio PA. Improving patient education with an eczema action plan: a randomized controlled trial. *JAMA Dermatol* 2013; **149**: 481–483.