DOI: 10.1111/jdv.16892 JEADV

POSITION STATEMENT

ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children

A. Wollenberg,[1,*] S. Christen-Zäch,[2] A. Taieb,[3] C. Paul,[4] J.P. Thyssen,[5] M. de Bruin-Weller,[6] C. Vestergaard,[7] J. Seneschal,[8] T. Werfel,[9] M.J. Cork,[10] B. Kunz,[11] R. Fölster-Holst,[12] M. Trzeciak,[13] U. Darsow,[14,15] Z. Szalai,[16] M. Deleuran,[7] L. von Kobyletzki,[17,18] S. Barbarot,[19] A. Heratizadeh,[9] U. Gieler,[20] D.J. Hijnen,[21] S. Weidinger,[12] L. De Raeve,[22] Å. Svensson,[23] D. Simon,[24] J.F. Stalder,[25] J. Ring,[14,26], for the European Task Force on Atopic Dermatitis/EADV Eczema Task Force[,†]

[1]Department of Dermatology and Allergy, Ludwig-Maximilian-University, Munich, Germany
[2]Pediatric Dermatology Unit, Departments of Dermatology and Pediatrics, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
[3]University of Bordeaux, Bordeaux, France
[4]Department of Dermatology and Allergy, Toulouse University and CHU, Toulouse, France
[5]Department of Dermatology and Allergy, Herlev-Gentofte Hospital, University of Copenhagen, Hellerup, Denmark
[6]National Expertise Center for Atopic Dermatitis, Department of Dermatology and Allergology, University Medical Center, Utrecht, The Netherlands
[7]Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark
[8]Department of Dermatology, National Reference Center for Rare Skin Diseases, Bordeaux University Hospitals, Bordeaux, France
[9]Division of Immunodermatology and Allergy Research, Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany
[10]Sheffield Dermatology Research, IICD, University of Sheffield, UK
[11]Dermatologikum Hamburg, Hamburg, Germany
[12]Department of Dermatology and Allergy, University Hospital Schleswig-Holstein, Kiel, Germany
[13]Department of Dermatology, Venereology and Allergology, Medical University of Gdansk, Gdansk, Poland
[14]Department of Dermatology and Allergy Biederstein, Technische Universität München, Munich, Germany
[15]ZAUM – Center of Allergy & Environment, Munich, Germany
[16]Department of Dermatology, Heim Pál National Children's Institute, Budapest, Hungary
[17]School of Medical Sciences, Lund University, Malmö, Sweden
[18]School of Medical Sciences, Örebro University, Örebro, Sweden
[19]Department of Dermatology, CHU Nantes, UMR 1280 PhAN, INRA, F-44000, Nantes Université, Nantes, France
[20]Department of Dermatology, University of Gießen and Marburg GmbH, Gießen, Germany
[21]Department of Dermatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[22]Department of Dermatology, Universitair Ziekenhuis Brussel (UZB), Free University of Brussels (VUB), Brussels, Belgium
[23]Department of Dermatology, Skane University Hospital, Malmö, Sweden
[24]Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[25]Department of Dermatology, CHU Nantes, UMR 1280 PhAN, INRAE, F-44000, Nantes Université, Nantes, France
[26]Christiane-Kühne Center for Allergy Research and Education (CK-Care), Davos, Switzerland
*Correspondence: A. Wollenberg. E-mail: wollenberg@lrz.uni-muenchen.de

Abstract

Atopic dermatitis (AD) is a highly pruritic, chronic inflammatory skin disease. The diagnosis is made using evaluated clinical criteria. Disease activity and burden are best measured with a composite score, assessing both objective and subjective symptoms, such as SCORing Atopic Dermatitis (SCORAD). AD management must take into account clinical and pathogenic variabilities, the patient's age and also target flare prevention. Basic therapy includes hydrating and barrier-stabilizing topical treatment universally applied, as well as avoiding specific and unspecific provocation factors. Visible skin lesions are treated with anti-inflammatory topical agents such as corticosteroids and calcineurin inhibitors (tacrolimus and pimecrolimus), which are preferred in sensitive locations. Topical tacrolimus and some mid-potency corticosteroids are proven agents for proactive therapy, which is defined as the long-term intermittent anti-inflammatory therapy of frequently relapsing skin areas. Systemic anti-inflammatory or immunosuppressive treatment is a rapidly changing

[†]See Appendix section.

field requiring monitoring. Oral corticosteroids have a largely unfavourable benefit–risk ratio. The IL-4R-blocker dupilumab is a safe, effective and licensed, but expensive, treatment option with potential ocular side-effects. Other biologicals targeting key pathways in the atopic immune response, as well as different Janus kinase inhibitors, are among emerging treatment options. Dysbalanced microbial colonization and infection may induce disease exacerbation and can justify additional antimicrobial treatment. Systemic antihistamines (H1R-blockers) only have limited effects on AD-related itch and eczema lesions. Adjuvant therapy includes UV irradiation, preferably narrowband UVB or UVA1. Coal tar may be useful for atopic hand and foot eczema. Dietary recommendations should be patient-specific, and elimination diets should only be advised in case of proven food allergy. Allergen-specific immunotherapy to aeroallergens may be useful in selected cases. Psychosomatic counselling is recommended to address stress-induced exacerbations. Efficacy-proven 'Eczema school' educational programmes and therapeutic patient education are recommended for both children and adults.

Received: 18 June 2020; revised: 10 July 2020; Accepted: 23 July 2020

Conflicts of interest

AW has been a principal investigator, advisory board member or consultant for AbbVie, Almirall, Galderma, Hans Karrer, Leo Pharma, Lilly, MedImmune, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., and Sanofi Genzyme, and received speaker honoraria from Chugai, Galderma, Leo Pharma, Lilly, Loreal, MedImmune, Pfizer, Pierre Fabre, Regeneron Pharmaceuticals, Inc., and Sanofi Genzyme. SCZ has been an advisor, speaker or investigator for Galderma, L'Oreal, La Roche Posey, Pierre Fabre, Procter and Gamble and Sanofi Genzyme. AT has been consultant or investigator for Pierre Fabre, Galderma, Novartis, Johnson and Johnson, Incyte, AbbVie, Modilac, Pfizer, Lilly, Arena, Bioderma and Sanofi. CP has been investigator or consultant for AbbVie, Almirall, Astellas, Boehringer, Bristol-Myers Squibb, Celgene, Eli Lilly, Galderma, Janssen Cilag, Leo Pharma, Merck, Novartis, Pierre Fabre, Pfizer, Regeneron, Sanofi and UCB. JPT has been an investigator/advisor/presenter for AbbVie, Regeneron, Sanofi Genzyme, Leo Pharma, Eli Lilly & Co and Pfizer. MdB has been a principal investigator, consultant and advisory board member for AbbVie, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, Leo Pharma and Pfizer. She has been an advisory board member and consultant for Eli Lilly and an advisory board member for Galderma and UCB. CV has received honoraria and research grants from Leo Pharma, Sanofi, Novartis, AbbVie and Eli Lilly. JS has received honoraria for lectures and advisory boards from AbbVie, Leo Pharma, Eli Lilly, Novartis, Pfizer, Pierre Fabre and Sanofi Genzyme. TW has received lecture or consultancy fees from AbbVie, Almirall, Astellas, Galderma, Janssen/JNJ, Leo Pharma, Lilly, Novartis, Pfizer and Regeneron/Sanofi. MJC is an Investigator and Consultant for Regeneron, Sanofi Genzyme, Pfizer, Leo, Galapagos, Novartis, Boots, L'Oreal, Dermavant, Menlo, Reckitt Benckiser, Oxagen, Johnson & Johnson, Hyphens, Astellas, Eli Lilly, AbbVie, Galderma and Procter & Gamble. BK has been a speaker, investigator or member of scientific advisory board for La Roche Posay, Beiersdorf, Procter and Gamble and Pierre Fabre. RFH reports being a consultant/advisor for Beiersdorf AG, Johnson & Johnson, Leo Pharma, Neubourg, Novartis Pharma AG, Nutricia, Pfizer Inc., Regeneron and Sanofi-Aventis as well as speaker for Beiersdorf AG, Leo Pharma, Neubourg, Novartis Pharma AG, Pierre Fabre Laboratories, Pfizer, Procter & Gamble, Regeneron and Sanofi-Aventis. MT has been an advisor, investigator or speaker for La Roche Posey, Leo Pharma, Pfizer, Pierre Fabre and Sanofi Genzyme. UD gave advice to or received an honorarium for talks or research grant from the following companies: ALK-Abello, Bencard, Meda, Novartis and Sanofi-Regeneron. SZ has performed consultancies for Sanofi Genzyme, Regeneron, Leo Pharma and Novartis; has lectured at educational events sponsored by Nutricia; and is involved in performing clinical trials with pharmaceutical industries that manufacture drugs used for the treatment of psoriasis and atopic dermatitis. MD has been a principal investigator, speaker, advisory board member and/or consultant for Leo Pharma, AbbVie, Almirall, Lilly, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, Morphosys-Galapagos, Pierre Fabre and MEDA. LvK has been investigator, speaker or consultant for Pfizer, Sanofi, Leo Pharma and Eli Lilly. SB has been a principal investigator, advisory board member or consultant for Pierre Fabre, Bioderma, La Roche Posay, Sanofi Genzyme, AbbVie, Novartis, Janssen, Leo Pharma, Pfizer, Amgen and Lilly. AH received lecture or consultancy fees from Leo Pharma, Novartis, Pierre Fabre, Sanofi- Genzyme, Beiersdorf, Hans Karrer, Nutricia, Meda and Lilly and a travel grant from Janssen. UG reports no conflict of interest. DJH has been investigator, speaker or consultant for AbbVie, Eli Lilly, Incyte, Leo Pharma, MedImmune/AstraZeneca, Pfizer, Sanofi and Thermo Fisher. SW has received institutional research grants from Leo Pharma and L'Oreal; has performed consultancies for Sanofi Genzyme, Regeneron, Leo Pharma, Incyte, Lilly, AbbVie and Novartis; has lectured at educational events sponsored by Sanofi Genzyme, Regeneron, Leo Pharma, AbbVie and Galderma; and is involved in performing clinical trials with pharmaceutical industries that manufacture drugs used for the treatment of atopic dermatitis. LDR is a consultant, member of scientific

advisory boards and/ or received personal fees and non-financial support from Leo Pharma, Pierre Fabre, Sanofi Genzyme and Bioderma. DS has been an investigator, advisory board member or consultant for AbbVie, AstraZeneca, Galderma, Lilly, Pfizer, Roche Pharma and Sanofi Genzyme. JFS, JR and AS reports no conflict of interest.

Funding sources

None.

This article is the 4th edition of the European Task Force on Atopic Dermatitis (ETFAD) of the European Academy of Dermatology and Venerology (EADV) position paper. Like the earlier versions,[1–3] it communicates the experience, opinion and recommendation of the ETFAD on the current treatment and management options for atopic dermatitis (AD) in view of recently updated relevant guidelines,[4,5] position papers[6] and relevant original data from the point of view of care-giving expert physicians regularly involved in managing patients with AD. It is by intention neither a guideline, nor a systematic review, but a short expert opinion paper communicating clinically useful information for diagnosing and treating AD.

Introduction and definitions

Atopic dermatitis (syn. atopic eczema, eczema, neurodermitis) is an inflammatory, chronically relapsing and intensely pruritic skin disease often occurring in families with atopic diseases (AD, food allergy, bronchial asthma or allergic rhinoconjunctivitis). The current understanding indicates that AD is a systemic T-helper (Th) 2-driven disease, in which the prevalence of atopic comorbidities is high, in particular in patients with moderate-to-severe AD.[7] From a clinical and histopathological standpoint, AD is an eosinophilic/spongiotic inflammation of the skin with characteristic age-dependent distribution patterns and morphology of lesions. With a prevalence of 2%–10%[8] in young adults and up to 20% in children, AD is one of the most common skin diseases. The varying aetiologic concepts of this disease are mirrored by the different names that are or have been used, such as 'neurodermatitis', 'neurodermitis' and 'endogenous/constitutional eczema'.

Atopy can be defined as familial hypersensitivity of the skin and the mucosa to environmental substances, associated with increased production of immunoglobulin E (IgE) or altered pharmacologic reactivity.[9] The ETFAD defines atopy as the 'familial tendency to develop Th2 responses against common environmental antigens', which keeps both IgE-associated, extrinsic and non-IgE-associated, intrinsic subtypes[10] within the definition of atopy.

The atopic diseases are genetically linked, and the concordance in monozygotic twins is 80% vs. 30% in dizygotic twins.[11] Described genetic polymorphisms in AD involve mediators of atopic inflammation on different chromosomes, and some of these are also relevant for respiratory atopy. The strongest association has been shown with mutations in the filaggrin gene also associated with ichthyosis vulgaris, highlighting the predisposing barrier defect in AD patients.[12] Concomitant ichthyosis vulgaris can be diagnosed clinically, and increased palmar hyperlinearity is a good indicator of filaggrin gene mutations.[13] In the first months of life, a yellowish layer of seborrhoeic, crusted scales on the scalp, known as 'cradle cap', may be the first presentation of AD and can be treated with emollients only. AD usually starts in the face, with middle face sparing, and on the extensor surfaces of the arms and legs of toddlers, as well as the trunk, sometimes showing extensive oozing and crusting. Later on, eczematous involvement of flexures, neck and hands predominates, accompanied by dry skin. The skin barrier dysfunction is reflected by an increased transepidermal water loss (TEWL).[14] Measuring TEWL with an evaporimeter and discussing the results with the patient will increase adherence to recommended emollient therapy. Lichenification is the result of scratching and rubbing, frequently at night-time. The prurigo type of AD is associated with predominant excoriated, nodular and lichenified lesions. Exacerbations often start as increased itch without visible skin lesions, followed by erythema, papules and infiltration. As histopathologic features are not specific for AD, routine histology is not useful for diagnosing AD, but may help to rule out differential diagnoses, such as cutaneous T-cell lymphoma in adults.[3]

In the absence of a specific diagnostic laboratory marker, AD is diagnosed clinically. The diagnostic power of an experienced clinician is superior to all diagnostic criteria available, but standardized criteria are needed for epidemiological research, as well as for inclusion criteria for clinical trials. Most diagnostic criteria are based on cutaneous signs of atopy.[9,15] Hanifin and Rajka's criteria include pruritus, typical morphology and distribution, chronic or chronically relapsing course, and atopic personal or family history (3 of 4 necessary), in addition to 3 minor criteria among a list of 21.[15] According to the UK working party criteria, itchy skin changes have to be diagnosed in the last 12 months, in addition to at least three of the following criteria: onset of the disease under the age of two years, history of involvement of skin folds, generalized dry skin, other atopic diseases and visible flexural eczema.[16]

Atopic dermatitis has a profound impact on all dimensions of the patient's life.[17,18] Moderate-to-severe AD is associated with depression, anxiety, reduced quality of life, impaired self-esteem

and suicide.[19] The social impact of moderate-to-severe AD is high and similar to the one of psoriasis, chronic obstructive bronchitis, cardiovascular disease and diabetes.[20]

Management of acute exacerbations (flares) of AD is a therapeutic challenge, as it requires efficient short-term control of acute symptoms, without compromising the overall management plan that targets long-term stabilization, flare prevention and avoidance of side-effects. Exacerbation may sometimes uncover relevant provocation factors, such as underlying allergies or infection. Consequently, the initial workup must include a detailed inquiry on the circumstances of the flare, and a careful dermatologic examination including lymph nodes, orifices and all skin folds. Professional attitude in face of exacerbated disease is setting the stage for future adherence.[21] Patients often have their own beliefs about the origin of their flare, but disparaging remarks at this time will only increase patient or parental frustration with conventional medicine. Patient fears regarding treatment side-effects must be taken seriously with a compassionate attitude. Therapeutic patient education is an extremely helpful tool to address patient beliefs and questions regarding disease and treatment.[22]

Assessment of disease activity

As atopic dermatitis is a chronic disease, long-term management strategies are essential to consider. Consensus definitions for management procedures are necessary.[23] In clinical trials, three methods have been used to assess long-term control: repeated measurement of AD outcomes, amount of medication used and recording of AD flares/remissions.[24]

The notion of intolerance or resistance to topical treatments is a clinically meaningful soft term for inadequate AD improvement using potent topical corticosteroids (TCS) with intolerable long-term side-effects. As quantitative rules for prescription of topicals are rarely applied, it is difficult to refer to an upper limit to define resistance.[3] Very often, patients apply too little amounts of TCS leading to the perception of a lack of effect.

Overall disease activity should assess both objective and subjective symptoms, as both contribute to clinical severity.[3] This can be achieved with the SCORAD index.[25] Mild AD corresponds to SCORAD levels below 25 and severe AD to SCORAD levels above 50.[26]

Flare is a clinically meaningful term difficult to delineate.[27] Repeated measurements and arbitrary cut-offs of an existing severity scale, such as SCORAD,[25] measured at sequential intervals by physicians, have been used most frequently in the past.[27] However, defining flares based on the intensity of itch is difficult, as the level of tolerance to pruritus can vary largely.[3] Some patients with highly lichenified lesions report only moderate pruritus and insomnia. The amount of medication used by the patient can be measured to detect variations or flares. Novel tools for patient use like the patient-oriented (PO) validated scoring system PO-SCORAD may detect changes in signs and symptoms.[28] A valid, reliable and feasible flare definition acceptable for all clinical and research settings has still not been consented.[27] The ETFAD definition of flare is 'acute, clinically significant worsening of signs and symptoms of AD requiring therapeutic intervention' (see Table 1 for ETFAD definitions). Primary clinical outcome measures used in recent development programmes include the achievement of clear or almost clear skin (investigator global assessment of 0 or 1) or a 75% improvement in severity scores such as 'Eczema Area and Severity Index' (EASI) or SCORAD.[29] In addition, clinically relevant improvement in itch, as defined by a 3- to 4-point improvement in the 10-point itch numerical rating scale, is desirable.

Maintaining a long-term remission is a shared objective in chronic disorders. A widely accepted and uniform nomenclature would help to compare data. Long-term remission without lesions and treatment is usually synonym of cure, but the time without intervention that may correspond to such a situation is still to be defined. Remission achieved by the avoidance of irritants and allergens with sole emollient use is not comparable to remission under immunosuppressive agents or biologics (Table 1). Other proposals come from asthma management (weeks with complete control/ weeks with good control) or from pragmatically oriented judgement (increase in treatment, medical visit or call).[30] Kaplan–Meier diagrams comparing flare-free percentages of study populations using study drug and control for 1 year (or at least 3 months) is a clinically meaningful visualization for flare prevention studies.[3] Data extraction of 'percent patients flared at study end' from treated patients may produce misleading meta-analysis results,[31] whereas prolongation of time to first flare in 50% of treated vs untreated patients, or comparing the percentage of flare-free patients at a fixed time (e.g. 12 weeks), is recommended.[32] Long-term control scores for use in clinical trials have recently been developed by international teams.[33]

Basic therapy for atopic dermatitis and skincare

Since AD is a chronic condition, treatment has to be planned with a long-term perspective and special attention must be given to long-term safety aspects.

Cleansing

The skin must be cleansed thoroughly, but gently and carefully to get rid of crusts and mechanically eliminate bacterial contaminants, especially in the case of bacterial superinfection. Cleansers with or without antiseptics in non-irritant and low allergenic formulas may be used in various galenic forms such as syndets or aqueous solutions. As the duration of action of some antiseptics is very limited, mechanical cleansing is probably more important.[34] The pH should be in a physiological cutaneous

(a) Treatment of atopic dermatitis: adult

- For every grade, *additional* therapeutic options are given
- Add antiseptics / antibiotics in cases of superinfection
- Consider compliance and diagnosis, if therapy has no effect
- Refer to full 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; short course of cyclosporin A[1,2], dupilumab [2], short course of oral glucocorticosteroids [1,2]; longer course of systemic immunosuppression: 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] topical crisaborole [3]
BASELINE Basic therapy	Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests)

(b) Treatment of atopic dermatitis: children

- For every grade, *additional* therapeutic options are given
- Add antiseptics / antibiotics in cases of superinfection
- Consider compliance and diagnosis, if therapy has no effect
- Refer to full 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; dupilumab [1,2]; course of systemic immunosuppression: cyclosporin A [3], methotrexate [3], azathioprin [3], mycophenolate mofetil [1,3]
MODERATE: SCORAD 25-50 / or recurrent eczema	Proactive therapy with topical tacrolimus [2] or class II or class III topical glucocorticosteroids [3], wet wrap therapy, UV therapy [1] (UVB 311 nm), 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] topical crisaborole [3]
BASELINE Basic therapy	Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests)

Figure 1 The treament recommendations according to the ETFAD member consensus for adults (a) and children (b) based on the severity of the disease

range around 5–6, but if possible, lower pH products are generally good for the skin barrier. A small randomized study did not show any difference in bathing twice weekly or everyday with respect to AD severity,[35] as long as hydration of skin is managed after the bath. However, longer duration of the bath is associated with worsening of the symptoms.[36]

Table 1 Definitions of descriptive items for the management of AD

Flare: Acute, clinically significant worsening of signs and symptoms of atopic dermatitis requiring therapeutic intervention.
Instrument: A unidimensional or multidimensional scoring system used to measure relevant items of a disease. The EASI, objective SCORAD, POEM and DLQI are validated instruments for signs, symptoms or quality of life of AD, whereas the SCORAD is a validated composite score assessing both signs and symptoms of AD.
Intolerance to topical treatment: Patient's opinion after at least 2 weeks of therapy with a new topical treatment, because of worsening of lesions or any difficulty to apply the drug (ointment not supported, pain, burning or any uncomfortable sensation).
Items: Measurable disease-related features can be either or both signs and symptoms.
Proactive therapy: Long-term, low-dose intermittent application of anti-inflammatory therapy to the previously affected skin, together with an ongoing emollient treatment of unaffected skin.
Remission/Control: Period without flare of at least 8 weeks without anti-inflammatory treatment (irritant/allergen avoidance and emollient use not included).
Complete remission: If using basic treatment (avoidance, emollients)
Incomplete remission: If using moderate treatment, topical corticosteroids or calcineurin inhibitors less than 30 g/month in children and less than 60 g/month after 15 years of age
Control: If using major treatment including phototherapy or immunosuppressants
Severity of disease: The overall impact of signs and symptoms of AD on a patient, which requires assessment with a composite score.
Mild disease: If SCORAD is <25
Moderate disease: If SCORAD is ≥25 and <50
Severe disease: If SCORAD is ≥50
Sign: A disease-related item captured by an observer. It has the potential to be objective and reproducible. Signs of AD may be assessed by EASI and objective SCORAD.
Symptom: A disease-related item captured by a patient. It is by definition subjective. Most symptoms mirror signs or other symptoms. Symptoms of AD may be assessed by POEM.
Resistance to topical treatment: Physician's opinion of a situation with unchanged or aggravated clinical score after at least 2 weeks of appropriately dosed and performed treatment.

The most important aspect of washing in AD is the avoidance of all harsh detergents and alkaline soap. The alternatives include emollient wash products (bath oils, shower emollient wash products) or using a leave-on emollient cream as a wash product.

Emollient bath additives for the treatment of childhood eczema showed no clinical benefit if used in addition to using leave-on emollients as a soap substitute.[37] The latter combination is rarely used in reality. The ideal is to let patients choose which emollient wash products they prefer, as this will be the one they will use. Topical emollients are preferentially applied immediately after a bath or a shower following gentle drying when the skin is still slightly humid, which is known as 'soak-and-seal' technique.[34] Although bathing seems very important, there is lack of good evidence to prove its effectiveness or specific parameters of use.

The ETFAD recommends regular bathing or showering in warm but not hot water about 2–7 times per week with very mild surfactant and emollient-based wash products in a 'soak-and-seal' approach.

Emollient therapy

Atopic dermatitis is associated with skin barrier anomalies that facilitate an easier allergen penetration into the skin with an increased proneness to irritation and subsequent cutaneous inflammation. A lack of important stratum corneum intercellular lipids and an inadequate ratio between lipid compounds (cholesterol, essential fatty acids, ceramides), as well as filaggrin defects,[12] enhance TEWL. This leads to epidermal micro-fissuring, which may also cause direct exposure of Langerhans cell dendrites as well as nerve endings to the environment. A better molecular and biochemical knowledge on this predisposing background should provide access to barrier improving topical agents. The use of high-quality emollients can be cost-effective because they prevent the development of flares and the need for anti-inflammatory TCS and TCI.[38] Nevertheless, if an acute flare does occur, it is better to treat with anti-inflammatory topicals first as outlined below, instead of applying emollients to acute inflamed lesions.[39,40]

Emollients are not always beneficial, as some can lead to other skin sensory adverse events such as burning, stinging or pruritus, especially if the emollients are used on inflamed skin. About 1/3 of adult AD patients have developed contact allergies to ingredients of their emollients and type IV sensitization to emulsifiers, preservatives and fragrances being the most common.[41] In patients with this problem, it is best to use the simplest emollient ointment formulations with the smallest number of ingredients.

By tradition, emollients are defined as topical treatment with vehicle-type substances lacking active ingredients. Most of them contain a humectant (promoting stratum corneum hydration, such as urea or glycerol) and an occludent (reducing evaporation, such as petrolatum).[4] Urea is known to significantly reduce the risk of AD relapse.[38]

Several non-medicated products for topical treatment of AD contain putative active ingredients, but are neither fulfilling the definition of nor needing a licence as a topical drug. These products, referred to as 'emollients plus' by the European guideline, may contain, for example, flavonoids such as licochalcone A, saponins and riboflavins from protein-free oat plantlet extracts, bacterial lysates from *Aquaphilus dolomiae* or *Vitreoscilla filiformis* species, or a synthetic derivative of menthol such as menthoxypropanediol.[4,42] Emollients containing potentially allergenic plant *proteins* from peanut, oat or wheat should be avoided in children before the age of 2,[43] whereas protein-free plant extracts are apparently safe to use.[44]

The ETFAD recommends the daily use of liberal amounts of emollients, at least 30 g/day or 1 kg/month for an adult, which should preferentially be applied in a 'soak-and-seal' technique (Fig. 1).

Primary prevention

Primary prevention targets the general or an at-risk population with preventive measures, if there is still no evidence of disease.

Emollients have recently been recommended for primary prevention of AD,[45] but there are conflicting data. On one hand, two pilot randomized trials showed a 32% and 50% relative risk reduction in incident AD by the daily use of emollients from birth in neonates who are at high risk of developing AD.[46–48] On the other hand, two recently published larger and longer trials with a less stringent intervention did not confirm these effects of emollients.[49,50] Though emollients are a mainstay of AD treatment, the role for primary prevention of AD is unclear at present.

Probiotics (inactivated bacteria) and prebiotics (fibres that can promote the growth of certain bacteria in the gut) have been studied for primary prevention of AD during pregnancy or in neonates, but older data were essentially inconclusive. A diagnosis of AD is associated with a decreased diversity of neonates' gut microbiota.[51] A new Cochrane systematic review and meta-analysis of 21 studies issued the recommendation that a mixture of probiotic supplementation given to the mother during pregnancy and continued, while breastfeeding would be most efficacious in reducing the risk of incidence of AD in children.[52,53]

The ETFAD does not give a recommendation for any dietary and lifestyle changes aiming at primary prevention of AD, because the quality of data is not sufficient to issue a sustainable recommendation for any of the interventions studied.

Avoidance strategies based on a diagnosis of allergy

Atopic dermatitis is associated in particular with immediate but also delayed-type hypersensitivity against environmental allergens. Among food allergens, cow's milk, hen's egg, wheat, soya, tree nuts and peanuts are most frequently associated with AD exacerbation in infants and toddlers. In older children, adolescents and adults, pollen-related food allergies should be taken into account.[54] Irritant factors comprising chemicals and physical agents may complicate the course of the disease. Finally, contact sensitization to chemicals, drugs, plants or metals is as frequently found in AD as in non-atopic individuals and may complicate the clinical severity by overlying allergic contact dermatitis.[55] Diagnosing the individually relevant trigger factors for AD is more challenging than diagnosing the disease.

The ETFAD recommends an allergy workup for moderate-to-severe AD patients, which may include serum IgE, skin prick tests and patch tests for contact sensitization to ingredients of emollients and topical anti-inflammatory agents, depending on the individual history. Mild patients may be tested depending on clinical suspicion.

Food allergens

About one-third of children with a moderate-to-severe AD have an associated food allergy.[56] It is a common misconception that food allergy would be causative in the setting of AD. Parents must be warned that general elimination diets are not recommended,[57] and can be detrimental.[58] In AD children with proven food allergy, good skincare is also the mainstay of treatment, but identifying and avoiding trigger factors are important.[57]

Sensitizations to foods can be identified by means of in vivo tests (skin prick tests, prick-prick tests) and in vitro tests (serum specific IgE). A positive test indicates IgE-mediated sensitization, but may have poor correlation with clinical responses.[59] In addition, atopy patch tests proved to be useful for studying delayed food-related skin responses.[60]

A skin prick test (SPT) with food allergens (i.e. cow's milk, eggs, wheat, soya, peanut) is suggested in children <5 years with moderate-to-severe AD that is persistent in spite of optimized management and topical therapy. Food allergy is less common in older age groups. Tests are recommended when food allergy is suspected.

In vitro tests (i.e. specific IgE testing) are valuable when SPT cannot be applied because of *urticaria factitia* (urticarial dermographism), UV- and drug-induced skin hypo-reactivity or lack of compliance for SPT in infants.[61] Moreover, in vitro data of specific IgE to food allergens allow better quantitative grading of sensitization, which helps to estimate the probability of the risk of a clinical reaction and offers the opportunity to test single recombinant allergens, which may have a better diagnostic specificity than testing with food extracts. Importantly, skin prick test reactivity to foods seems to decrease during the first 7 years, whereas specific IgE against food allergens tend to increase.[62]

The atopy patch test (APT) for food allergens has been standardized for selected food and aeroallergens,[60,63] but preparations are expensive, not adequately reimbursed and also not approved for routine diagnosis by the authorities.[60] As a pragmatic alternative, the APT may be performed with self-made food material using large test chambers for 48–72 h, but these test materials are not standardized.[64] Whereas immediate-type reactions are associated with SPT positivity, delayed-type reactions are related to positive responses to APT.[65] However, food challenge cannot be replaced by patch testing.

The best method to prove clinically significant allergy is the double-blind placebo-controlled food challenge.[61] In clinical reality, elimination and reintroduction of a certain food after a reliable history can be sufficient. Oral challenging of AD patients with foods may induce early reactions such as urticaria, gastrointestinal or respiratory symptoms usually occurring within 30–120 min after allergen administration, or eczematous late-phase responses after 18–48 h. About 45% of oral food challenges result in both immediate and delayed reactions, whereas 12% showed worsening of eczema only.[66] The personal history has a low predictive value (30%) for oral challenge-induced late reactions, as opposed to 80% for immediate reactions.[66]

The ETFAD recommends that an elimination diet for AD should not be based on type I sensitization detected by blood or

skin prick tests, but on a reliable history followed by elimination and reintroduction of suspected food or an oral food challenge if this is feasible.

Aeroallergens

Clinical observations and experimental studies indicate that aeroallergens are relevant trigger factors in AD patients.[67] Exacerbations of eczematous lesions after skin contact or inhalation have been described, but studies on allergen avoidance strategies show conflicting results.[68] Routine diagnostic workup of suspected allergy to aeroallergens includes detection of specific IgE by means of skin prick tests or in vitro IgE assays. However, both techniques have a low predictive value.

Atopy patch test (APT) with aeroallergens targets the cellular component of AD,[63] and has been performed with house dust mites, pollen and animal dander, obtaining different positivity rates (15%–100%) according to patch test materials and modalities.[60] On the basis of the history of aeroallergen-triggered AD flares, APTs proved to have higher specificity and lower sensitivity than the above-mentioned tests[63] and may detect sensitization in skin prick test negative, 'intrinsic' AD patients.[65]

Unfortunately, standardized aeroallergen preparations are not available for routine testing in APT so far. As still no feasible standard procedure for provocation of eczema in aeroallergen-mediated AD exists, specific avoidance strategies should be considered for highly sensitized patients with chronic, moderate-to-severe disease on a patient individual basis (Table 2).

Contact allergy

Contact allergy may be detected in 40%–65% of AD patients and cause worsening of their skin lesions.[69] Factors favouring allergic contact dermatitis in AD patients include the prolonged and repeated exposure to ingredients of topical treatments, along with increased skin barrier penetration.[70] Emulsifiers, fragrances, preservatives, corticosteroids and other components of topical treatment preparations are the most relevant substances to be tested.[41,69] In addition, contact allergy to compositae plants should be considered, e.g. when severe facial eczema is observed during the summer months.[71] Children with AD who have long-lasting moderate-to-severe hand or foot dermatitis should always be patch-tested to evaluate whether they have an allergic contact dermatitis.[72] Patch testing of AD patients can be tricky, as Th2 inflammation may suppress contact allergy, which in turn requires physicians to test when the AD is under control.[73] Patch testing should be considered before systemic intervention is planned.[74] Patch testing of occupational allergens is discussed in a separate chapter below.

The ETFAD suggests setting a low threshold for performing patch tests with a standard series and components of topical treatment preparations in AD patients. In addition, patch testing is recommended in AD patients with recalcitrant disease, atypical localization or aggravation without known cause, especially when systemic intervention is considered.

Table 2 List of aggravating factors and counselling for AD patients

- Clothing: Avoid skin contact with irritating fibres (wool, large fibre textiles). Do not use tight and too warm clothing to avoid excessive sweating. New non-irritating clothing, designed for AD children and adults, and especially silver-coated textiles are encouraged
- Tobacco: avoid exposure
- Cool temperature in bedroom and avoid too many bed covers
- Increase emollient use with cold weather
- Avoid exposure to herpes sores. Urgent visit if flare of unusual aspect
- Vaccines: normal schedule in non-involved skin, including egg-allergic patients (see text)
- Sun exposure: no specific restriction with careful use. Usually helpful because of anti-inflammatory effect and improvement of epidermal barrier. Encourage summer holidays in high altitude or at beach resorts
- Physical exercise, sports: no restriction. If sweating induces flares of AD, progressive adaptation to exercise. Shower and emollients after swimming pool
- Food allergens
  - a Maintain breastfeeding until four months if possible; include all foods recommended for the given ages after 4 months, unless the child develops allergy symptoms or sensitization has been shown
  - b Otherwise normal diet, unless an allergy workup has proven the need to exclude a specific food
  - c Some patients show improvement by avoiding foods cross-reactive to pollen (e.g. birch pollen)
- Indoor aeroallergens
- House dust mites
  - a Use adequate ventilation of housing. Keep the rooms well-aerated even in winter
  - b Avoid wall to wall carpeting
  - c Remove dust with a wet sponge
  - d Vacuum with an adequate filtered cleaner once a week floors and upholstery
  - e Avoid soft toys in bed (cradle), except washable ones
  - f Wash bed sheets at a temperature higher than 55° every 10 days
  - g Bed and pillow encasings in Gore-Tex or similar
- Furred pets: Advice to avoid cats but not dogs preventively. If allergy to furred pets is demonstrated, be firm on avoidance measures
- Pollen: In sensitized individuals, close windows during peak pollen season on warm and dry weather and restrict if possible stays outdoors. Aeration at night and early in the morning or by rainy weather. Avoid exposure to risk situations (lawn mowing). Pollen filters in car. Clothes and pets can vectorize aeroallergens, including pollen.

Topical anti-inflammatory treatment

Effective topical therapy depends on three fundamental principles: sufficient strength, sufficient dosage and correct application.[2] Topical treatment should be applied on hydrated skin if possible, especially when using ointments. If emollients and anti-inflammatory topical preparations must be applied to the same location, the cream formulation should be applied first and only 15 min later the ointment formulation. Even without wet wraps, topical therapy is time-consuming: patients should plan 30 min for one session. One well-conducted treatment per

day is usually sufficient; oozing AD may require a few days with higher treatment frequency.[16]

Wet-wrap treatment

Children and adults with acute, oozing and erosive lesions sometimes do not tolerate standard topical application and should be treated with 'wet wraps' first until oozing stops.[34] Wet-wrap dressings with diluted TCS (e.g. 1 : 3 for class II and 1 : 5 for class III) are applied for up to 14 days (usually 3 days are sufficient) and are a safe crisis intervention treatment, with temporary systemic bioactivity of the corticosteroid as the only reported serious side-effects.[75,76] Specialized nurse care is desirable to monitor wet-wrap treatment and to guide caregivers and patients, as it is done in eczema schools.[77]

The ETFAD recommends wet-wrap treatment for AD patients in flare, or with acute, oozing and erosive lesions.

Corticosteroids

Topical corticosteroids (TCS) are still the first-line anti-inflammatory treatment option in AD.[5] There are different strengths of TCS (mild, moderate, potent or super-potent) and different formulations (creams, ointments, lotions or foams) available.[78] The choice of the TCS depends on the patient's age, disease severity and location of AD lesions. Super-potent TCS (group IV) are not generally recommended for AD treatment, especially not in children. For routine treatment of flares, once-daily application of a potent TCS is sufficient, usually for 3–5 days. TCS should be started as soon as the first signs of the flare appear. Itch is a key symptom for evaluation of response to treatment, and tapering should not be initiated before itch has disappeared.[1] With mild disease activity, monthly amounts in the mean range of 15 g in infants, 30 g in children and up to 60–90 g in adolescents and adults, associated with a liberal use of emollients, generally allow a good maintenance with SCORAD values below 15–20.[2]

Topical corticosteroids should not be applied to the face every day for more than one month, because it may induce skin barrier fragility and rosacea-like perioral dermatitis. Intermittent use will reduce the risk of side-effects. Applying TCS on the inside of the thighs, upper arms and breasts (in females) for longer periods may cause stretch marks, particularly in adolescents. The risk of ocular complications with TCS seems to be low. Potent and very potent TCS (groups III and IV) are more likely to cause transient depression of adrenal function than group I (mild) and group II (moderate strength) treatments.[79]

The most constructive way to use TCS and avoid steroid-related side-effects is not to spare them during acute flares, but through early TCS intervention combined with consequent baseline emollient skincare to stabilize the disease.[80] Later on, proactive therapy should be used in the long term (see proactive therapy chapter below). The consequences of under treatment might be more serious than those associated with TCS treatment.[81] The risk of inducing systemic side-effects is lower with the use of the relatively new topical steroids with short half-life, such as prednicarbate, fluticasone and mometasone. A short-course, well-conducted systemic treatment may be safer and more advisable than prolonged use of high potency TCS for AD. Trials for TCS treatment in children less than 2 years old are lacking as well as for long-term use of mid and high potency TCS in paediatric populations.[81,82] In practice, TCS are often used in combination therapies (emollients, TCI, topical antibiotics, cyclosporine A[83] or dupilumab[84]). Patients' and healthcare professionals' fear of side-effects of corticosteroids (corticophobia) is quite common and should be addressed.[85] The education of patients and healthcare professionals is required to increase adherence to treatments.[21]

The ETFAD recommends using TCS according to standard guidelines in combination with many other treatment modalities including patient education.

Topical calcineurin inhibitors

TCI show quite good anti-inflammatory and very good antipruritic effects, whilst lacking adverse effects associated with TCS such as skin atrophy. TCI are especially useful in sensitive skin areas and occlusive areas, and in patients who need long-term treatment.[78] Two TCI, tacrolimus ointment and pimecrolimus cream, are licensed for topical AD treatment. The anti-inflammatory effects result from an inhibition of proinflammatory cytokine production by T cells and mast cells, whereas part of their antipruritic effects are attributed to a specific effect on TRPV1 neurons in the skin.[86] Applying the treatment twice a day is more effective than just once for the treatment of flares.[87–90] The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a TCS with intermediate activity,[91] while the latter is clearly more active than 1.0% pimecrolimus cream.[92]

Both TCI are safe to use and licensed for children aged 2 and above, and for adults.[93,94] Even long-term safety data from a 4- and 10-year tacrolimus and a 5-year pimecrolimus study exists.[95,96] Off-label use in children below 2 years of age is very common.[94] The most frequently observed side-effect is a transient warmth sensation or transient burning at the application site during the first days of application.[87,92] It starts about 5 min after each TCI application and may last up to one hour, but intensity and duration typically decrease with twice daily application within one week to zero.[97] A few days of initial treatment with TCS before switching to TCI may reduce the burning sensation, and an overlap period of one week may be advisable. A transient flush sensation following alcohol uptake is observed in few TCI-treated patients, which can effectively be blocked by taking 500 mg acetylsalicylic acid about 30 min before alcohol consumption. Patient education on these potential side-effects is required for adherence.[21]

Viral skin infections such as eczema herpeticum or eczema molluscatum have been observed during TCI treatment.[98,99] In

patients experiencing recurrent eczema herpeticum, continuous prophylactic treatment with oral valaciclovir may be advisable.[100] None of the TCI induces skin atrophy.[101,102] This favours their use over TCS in delicate body areas such as the eyelid region, the perioral skin, the genital area, the axilla region or the inguinal fold and for topical long-term management. Clinical data do not indicate an increased risk of the induction of lymphoma or other types of malignancies,[94,103] or photocarcinogenicity,[95,104,105] for TCI, but UV protection, e.g. with sunscreens, is recommended for theoretical safety reasons.[93,94]

The ETFAD recommends first-line use of TCI in delicate body areas, with preference for pimecrolimus in mild AD, and for tacrolimus in moderate and severe AD and for long-term topical treatment. Off-label use below the age of 2 years is also recommended.

Tar derivatives – aryl hydrocarbon receptor agonists

Topical application of coal tar is one of the oldest therapies for AD, with long-standing but constantly declining clinical use and moderate efficacy.[3] Coal tar may restore filaggrin expression and counteract the Th2-mediated downregulation of skin barrier proteins by aryl hydrocarbon receptor (AHR) activation and STAT6 dephosphorylation, thus diminishing spongiosis, apoptosis and CCL26 expression in AD lesions.[106] The cosmetic acceptance of tar preparations is poor, but tar preparations may be considered in selected cases, for example those with lichenification. The use in infants is controversial.

Recently, a 12-week, double-blind, vehicle-controlled, randomized study was performed using various concentrations of tapinarof (GSK2894512; 5-[(E)-2-phenylethenyl]-2-(propan-2-yl) benzene-1,3-diol), an AhR-modulating agent in adult patients with AD (BSA 5%–35%).[107] The most effective treatment was the 1% formulation applied twice a day, with a statistically significant treatment success. The most frequent treatment-emergent adverse events were folliculitis and contact dermatitis. Tapinarof is currently not licensed in any country for AD or any other indication.

Topical phosphodiesterase 4 inhibitors

Phosphodiesterase 4 (PDE4) is a key regulator of inflammatory cytokine production in AD through the degradation of cyclic adenosine monophosphate.[108] A recent meta-analysis including 7 double-blind randomized clinical trials of topical PDE4 inhibitors vs vehicle treatment for 1869 patients with mild-to-moderate atopic dermatitis concluded that topical PDE4 inhibitors were effective and safe for patients with mild-to-moderate AD.[109]

The most extensively studied topical PDE4 inhibitor, crisaborole, was studied in two identically designed, vehicle-controlled, double-blind studies (28 days) in patients aged 2 years and older with mild or moderate AD. Despite a strong vehicle effect, more crisaborole-treated than vehicle-treated patients achieved an Investigator's Static Global Assessment (ISGA) score of clear or almost clear with ≥2-grade improvement.[110] Crisaborole ointment had a low frequency of treatment-related adverse effects over 48 weeks of treatment of patients with AD observed in a long-term safety study.[111] Clinical trials with crisaborole in very young children (3–24 months) and studies comparing the efficacy of crisaborole to TCS and TCI are running, but the results are not published. Crisaborole is licensed in the United States, but not marketed in the EU.

At present, no recommendation can be given regarding topical PDE4 inhibitors.

Proactive therapy

By tradition, topical anti-inflammatory therapy has been applied to lesional skin only and has been stopped or tapered down once visible lesions were cleared. This reactive approach has been complemented by the proactive treatment concept, which is defined as a long-term, low-dose, anti-inflammatory treatment applied to previously affected areas of skin, in combination with use of emollients on the entire body and an appointment schedule for clinical control examinations.[23] Proactive therapy will prolong the time to relapse.[32] The proactive, usually twice-weekly topical treatment of previously affected areas is started only after all visible lesions have successfully been treated, in addition to daily ongoing emollient therapy for both previously affected skin and unaffected skin.[32] Clinical trial data are available for the TCS methylprednisolone aceponate and fluticasone propionate for up to 3 months, and for tacrolimus ointment for up to 1 year.[112–115] As a rule, barrier disruption is lower with proactive therapy than with daily application, as it is lower with TCI than with TCS.[116] Both TCS and TCI showed an antipruritic effect, with TCI being superior to TCS.[117] The cost-effectiveness of proactive therapy with topical tacrolimus has been demonstrated, as well as a beneficial effect on quality of life and lower aeroallergen-specific IgE levels in patients using proactive therapy.[118,119] Clinical experience and indirect evidence from many trials suggest that tacrolimus ointment, as well as TCS of Niedner classes II and III, are good candidates for proactive treatment, whereas pimecrolimus cream and TCS of Niedner class I are less efficient.[32]

The ETFAD recommends the introduction of proactive therapy with TCI or TCS in patients with moderate-to-severe AD.

Phototherapy

Phototherapy is a topical treatment option to improve skin lesions, pruritus and sleeplessness in AD patients, with remission periods up to 6 months and no documented serious short-term side-effects.[120] In AD, phototherapy affects several factors such as the suppression of the antigen-presenting function of Langerhans' cells, induction of antimicrobial peptides, the induction of apoptosis of infiltrating T cells[121], a reduction in the colonization by *S. aureus* and Malassezia species[122] and a reduced antigen

presentation following an increased phototherapy-induced thickness of the stratum corneum.[123]

Phototherapy is frequently used for the treatment of AD, especially for the treatment of the chronic phase in adults.[120] Phototherapy is usually part of a complex treatment plan, i.e. a second-level treatment.[3]

UV treatments should not be used to treat acute, in particular oozing, lesions as this will often result in a worse outcome. Patients with acute flares should instead be treated with a standard regimen for some days before starting UV treatment.[3] Due to practical challenges, theoretical concerns and limited data on the use of phototherapy in children with AD, phototherapy is usually not considered in prepubertal children, although not contraindicated.[3,4] In practice, the limitations are the availability of UV light machines, feasibility and lack of efficacy on lesions on scalp and folds. Combined use of TCI with UV is still controversial, even if the initial warnings of an increased skin cancer risk have not been substantiated.[105,124]

Beside natural sunlight (NSL), phototherapy for AD may be useful with different artificial light sources: broad-spectrum UVB (280–315 nm), narrowband (nb-) UVB (311–313 nm), broadband UVA (UVA) (315–400 nm), UVA1 (340–400 nm), UVA1 cold light (with seawater baths) plus UVB (balneophototherapy) and psoralen plus UVA (PUFVA). UVA1 phototherapy can be applied as moderate-dose (MD) (50 J/cm^2) and low-dose (LD) (10 J/cm^2) regimen, whereas high dose (HD) (130 J/cm^2) is not recommended anymore for AD treatment. Using 308-nm monochromatic excimer light allows the treatment of only limited areas.[125] Though blue light has been used for AD in an uncontrolled trial,[126] treatment with longer wavelengths has not been carefully studied for AD and is therefore not recommended.

nb-UVB is indicated for chronic moderate forms of AD and seems to cause less erythema compared with broadband UV. Medium-dose UVA1 appears to be similarly effective as nb-UVB,[127] but is more time-consuming. Concomitant treatment with TCS, emollients and phototherapy should be considered in order to reduce flare-ups.

UV light can also be combined with a prior (oral or topical) administration of photosensitizing drugs (psoralens): the so-called PUVA (photochemotherapy). All UV treatments and, even more, photochemotherapy pose a long-term risk of development of skin cancer, together with the proven prematurely ageing of the skin.[120] There are some data that individuals with filaggrin deficiency are particular at risk.[128,129]

Photochemotherapy for AD treatment has largely been abandoned due to its proven carcinogenicity and the fact that most AD patients are young.[3] Oral PUVA has a number of side-effects, which may include nausea, headache, fatigue, burning skin, itching and irregular skin pigmentation as well as an increased risk of skin cancer,[120] so the risk/benefit ratio of full-body treatment is usually unfavourable. In contrast, the risk/benefit ratio of topical PUVA for palms and soles is usually favourable.

The ETFAD recommends concomitant nb-UVB or medium-dose UVA in combination with TCS or selected systemic therapy for the treatment of AD.

Allergen Immunotherapy in AD

The efficacy and safety of allergen immunotherapy (AIT) in AD have been demonstrated in case reports, smaller cohort studies and a few larger multicentre trials. It is evident that AIT may improve the course of AD in selected patients rather than being a general risk of deterioration of the disease as anticipated by some patients and researchers.[130] Favourable effects of AIT on disease symptoms of AD appear to be higher if accompanying relevant type I sensitizations are present, but only house dust mite-sensitized patients have been studied in larger studies.[131,132] Here, the data for subcutaneous immunotherapy are stronger when compared to sublingual therapy and patients with severe AD (SCORAD > 50) showed better results.[132]

Patients with a positive APT, a positive challenge reaction or a history of eczema flares during the corresponding season, may be preferred candidates for future studies on AIT with the eliciting allergen. Regarding routine care, AIT is currently not recommended as a general treatment option for AD, but may be considered for selected patients with house dust mite, birch or grass pollen sensitization and severe AD.[5] Importantly, AIT may well be used in AD when approved indications for this treatment (allergic rhinoconjunctivitis or allergic asthma) exist in the same patient.

The ETFAD does not recommend AIT as a general treatment option for AD. However, AIT may be considered for selected patients with house dust mite, birch or grass pollen sensitization, who have severe AD and a history of clinical exacerbation after exposure to the causative allergen or a positive corresponding atopy patch test.

Antihistamines

Systemic antihistamines targeting the histamine 1 receptor (H1R) are often used to reduce itch in acute AD flares, whereas topical application has only been studied for doxepin in AD. A few randomized controlled trials have been conducted which have shown only a weak or no effect in decreasing pruritus in AD.

Low-quality evidence indicated that H1R antagonists (H1RA) might be effective as 'add-on' therapy when compared to placebo.[133] Due to this analysis, fexofenadine may lead to a small improvement in patient-assessed pruritus, with probably no clinically relevant difference in the amount of treatment used to prevent eczema flares. Cetirizine and loratadine were not superior to placebo in terms of clinical signs or symptoms. Of note, in a frequently cited controlled study, cetirizine has not shown any effects on AD scores but a protective or inhibiting effect on

associated urticaria in AD patients.[134] Antihistamines are generally safe in use and may be tried to decrease pruritus and permit sleep during flares, but particularly the first generation of antihistamines may affect sleep quality. Therefore, long-term use of sedative antihistamines is not recommended. In fact, a recent retrospective study attributed a higher rate of attention-deficit/hyperactivity symptoms (ADHS) in children with AD and a history of medication with antihistamines.[135] Ongoing studies focus on the blockade of alternative histamine receptors such as H4RA, which may be more important in AD.[136,137]

In conclusion, there is not enough randomized control trial evidence to demonstrate the efficacy of topical antihistamines, including doxepin in the treatment of itch in AD.

The ETFAD does not recommend the general use of first- or second-generation H1RA for the treatment of pruritus in AD. H1RA may be tried for the treatment of pruritus in AD patients, if standard treatment with TCS, TCI and emollients is not sufficient. Long-term use of sedative H1RA in childhood is not recommended.

Systemic anti-inflammatory therapy

Systemic therapy is necessary if AD cannot be controlled sufficiently with appropriate topical treatments and UV light therapy. It can also be useful to reduce the total amount of TCS in patients who need large amounts of potent TCS for vast body areas over prolonged periods to control their AD.[138] Before starting a systemic treatment, it is important to rule out differential diagnoses such as cutaneous T-cell lymphoma, potential trigger factors such as allergic contact dermatitis and behavioural and educational reasons for poor responses.[74,139] Until recently, rather broad-acting immunosuppressants, such as systemic corticosteroids (SCS), cyclosporine A (CyA), azathioprine (AZA), mycophenolate mofetil (MMF), enteric-coated mycophenolate sodium (EC-MPS) and methotrexate (MTX), were the only systemic treatment options for difficult-to-treat AD.[140] These systemic immunosuppressants can roughly be divided into two groups: SCS and CyA have a rapid onset of action and can be used to treat flares of AD or to bridge the time until onset of action of slow-acting systemic immunosuppressants such as MTX, AZA and MMF/EC-MPS. Dupilumab is the first biologic specifically licensed for AD, and many other biologics and small molecules are in advanced stages of clinical development.[141] The following recommendations for systemic drugs are based on expert opinions and medical considerations and may differ from the legal licensing status and access routes, which are not uniform in European countries.

Systemic corticosteroids

Systemic corticosteroids (SCS) are rapidly effective, but have a largely unfavourable risk/benefit ratio.[3] SCS should only be used for 1–2 weeks for severe acute exacerbations due to the many long-term side-effects. A typical regimen for severe acute exacerbations would be methylprednisolone maximal 0.5 mg/kg/day for 1–2 weeks and tapering over 1 month.[3] Short courses of SCS without adequate tapering can lead to high rates of relapse or rebound of the disease. In severe chronic cases, starting another oral immunosuppressive therapy while tapering the SCS should be considered. SCS must not be used for long periods of time due to significant risk of severe side-effects.[3]

Cyclosporine A

Cyclosporine A (CyA) is frequently used and very effective for AD in both children and adults.[142] It is used at 3–5 mg/kg/day, divided into a morning dose and an evening dose. The dosage should be started at 5 mg/kg/day and can usually be tapered after 4–6 weeks to 2.5–3 mg/kg in the maintenance phase. CyA has a narrow therapeutic index and requires close monitoring of blood pressure and signs of renal impairment, especially in elderly patients. CyA is approved for systemic treatment of AD in adults in most European countries.[142] CyA may be used off-label for children or pregnant females.[6] Treatment duration usually varies from 3 months to 1 year, but some patients tolerate much longer low-dose CyA treatment very well.[143] CyA is usually considered as the first-line option for patients requiring immunosuppressive treatment,[142] although the drug survival for CyA is much shorter than for MTX.[143]

Methotrexate

Methotrexate (MTX) has a slow onset of action. The recommended therapeutic doses are between 10 and 25 mg once weekly in adults and between 0.2 and 0.5 mg/kg/week in children (maximum dose 25 mg/week).[3] MTX is about equally effective as AZA and CsA in adults and children. The maximal clinical efficacy of MTX is reached after 8–12 weeks. Some reports suggest that in adult patients, higher dose of MTX (between 15 and 25 mg/week) could be used to reach maximum efficacy. Moreover, MTX showed good long-term effectiveness just like AZA. MTX is often well-tolerated and available for oral and subcutaneous administration. Infections, gastrointestinal disturbances and, in rare cases, myelotoxicity may limit the use of MTX. Each MTX cycle should be followed by a folic acid substitution.[144–147] MTX is hepatotoxic and teratogenic, and women of childbearing potential must use effective contraception during therapy.[6]

Azathioprine

Azathioprine (AZA) has a slow onset of action, as the maximal clinical efficacy is reached after 8–12 weeks. A starting dose of 50 mg/day for 1–2 weeks is recommended in adults. Depending on acute adverse events such as gastrointestinal side-effects, liver enzyme elevation or haematological abnormalities, the dose can usually be increased to 2–3 mg/kg/day. Low thiopurine methyltransferase (TPMT) activity is associated with an increased myelotoxicity of AZA, but TMTP activity screening tests can

identify patients at risk before starting the treatment. If this test is not available, treatment can be started with half the dosage, whilst monitoring for side-effects. Although most clinical trials are of short duration, there is evidence that AZA is effective and safe for the treatment of AD for up to 5 years. However, drug survival is mainly limited due to side-effects.[145,148] AZA increased the risk of non-melanoma skin cancer and lymphoma in inflammatory bowel disease patients.[95,104,149,150] AZA may be used in children. In pregnant females, AZA should only be used on strict indication.[6,151,152]

Mycophenolate mofetil

Mycophenolate mofetil (MMF) has a slow onset of action. A dose of MMF at 2 g/day and EC-MPS at 1440 mg/day is commonly used. However, enteric-coated mycophenolate sodium (EC-MPS) is equally effective as CyA as maintenance treatment in patients with AD. MMF may be used in children,[5,152] and the recommended dose is between 20 and 50 mg/kg/day. Mild gastrointestinal side-effects and haematological abnormalities are frequently observed during MMF treatment, but the general security profile seems to be quite favourable, making it an unlicensed but clinically useful treatment alternative for severe AD patients, especially for maintenance therapy. MMF and EC-MPS are both teratogenic, and women of childbearing potential must use effective contraception during therapy.[6,148,152–154]

The ETFAD recommends an initiation of classical immunosuppressive therapy with CyA, MTX, MMF or AZA only if topical treatment is not an option. The treating physician should have experience with these substances, and the choice of drug should consider all relevant patient- and drug-related factors including the patient's comorbidity, expected onset of efficacy, planed duration of treatment and licensing status of the drug.

JAK Inhibitors in clinical trials

Janus kinase (JAK) inhibitors are fast-acting drugs, which suppress a wide range of pathways. There are multiple lines of evidence that the JAK-STAT signalling pathway plays a major role in AD. An advantage of inhibiting JAK1 is that it covers multiple cytokines involved in the pathophysiology of AD, including IL-4, IL-13, IL-31, TSLP and IL-22. A JAK1 inhibitor may therefore be effective where a more selective biologic such as Th2 blockers has been insufficiently effective, but more side-effects might be observed. Several oral JAK inhibitors are currently under investigation for the management of AD. More study data have been presented at congresses than have appeared in full publications in peer-reviewed journals. Some JAK inhibitors are already licensed for rheumatoid arthritis.

Baricitinib is an oral selective JAK1 and JAK2 inhibitor licensed for rheumatoid arthritis in many European countries. The results of three phase 3 studies investigating oral baricitinib at 1, 2 and 4 mg daily for the treatment of AD are published.[155] Two placebo-controlled monotherapy studies were conducted without the addition of TCS (except as rescue therapy). 36% of patients achieved EASI 75 with baricitinib 4mg daily at week 16 without censoring for TCS rescue. In the third study, 47.7% of patients achieved EASI 75 when baricitinib 4mg daily was added to standard care TCS at week 16.[155] The most frequent adverse events were upper respiratory tract infections, headaches and an increase in blood creatine kinase.

Upadacitinib (ABT-494), an oral selective JAK1 inhibitor, showed reduction in pruritus as early as week 1 and improvement of the extent and severity of skin lesions as early as week 2 in a phase 2b trial.[156] At week 16, 69% and 50% of the patients achieved EASI 75 and EASI 90, respectively, with 30 mg daily. The most common relevant adverse events were upper respiratory tract infections and acne.[156]

Abrocitinib (PF-0496582) is another oral selective JAK1 inhibitor, which showed positive results in a phase 2b study.[156] Reduction in the EASI score was 82.6% for patients receiving 200 mg daily. 65% and 52% of the patients achieved EASI 75 and EASI 90, respectively, with 200 mg daily.[157] The most frequently reported, relevant adverse events were upper respiratory tract infections. Dose-dependent decreases in platelet count were observed but would recover back towards baseline levels after week 4.

JAK inhibitors are promising, fast-acting and potent therapies for the treatment of adult and adolescent AD. Dose selection for chronic treatment and long-term safety profiles will be important to assess, considering the potential risk of malignancies, serious infections and venous thrombosis. The more selective JAK1 inhibitors targeting only JAK1 may have less unwanted drug effects than the less specific JAK inhibitors.

The ETFAD recommends checking on a regular basis all upcoming information on JAK inhibitors, as the licensing of new drugs for the treatment of AD is likely.

Alitretinoin

Alitretinoin offers anti-inflammatory and anti-proliferative effects. One large trial involving 1032 chronic hand eczema patients,[158] about one-third of which are probably atopic hand eczema patients, as well as a small case series of six AD patients[159], indicate that this teratogenic drug is effective in atopic hand eczema and that bystander improvement of extrapalmar AD lesions is likely. Alitretinoin may be considered in adult atopic hand eczema patients unresponsive to TCS,[3] but is strictly contraindicated in pregnant women.[6]

Maternal and paternal exposure to oral immunosuppressive drugs

The maternal benefit of oral immunosuppressive drugs in expecting AD patients must always be weighed on an individual basis against possible adverse effects such as spontaneous abortion, prematurity, low birthweight, adrenal insufficiency, infections and teratogenicity.[6] Treatment with CyA and SCS is well

possible during pregnancy, but the unfavourable risk/benefit ratio of SCS remains.[3] MTX, alitretinoin, MMF and EC-MPS are strictly contraindicated in pregnancy. Continuation of AZA treatment (halved dose) is considered possible on strict indication.[6]

Detailed ETFAD recommendations for the treatment of AD in pregnant women have been published in 2019.[6]

The relationship of paternal use of oral immunosuppressive drugs before fathering and congenital abnormalities is less clear than the effects of maternal use. Although studies are often small and of poor quality, several guidelines recommend for menusing AZA or MPA to adequately use contraceptive measures during treatment and for three months thereafter.[160] It is recommended to wait three months after stopping MTX before fathering.

Biologics

Although AD is considered to involve multiple immune pathways potentially underlying different disease subtypes, a strong activation of type 2 immune responses, driven by innate type 2 lymphoid cells and type 2 T-helper cells with their signature cytokines IL-4, IL-5 and IL-13, appears to be a dominant mechanism.[141] Targeting type 2 pathways is therefore a reasonable therapeutic strategy.

Dupilumab

Dupilumab is the first biologic that has been approved as first-line treatment for moderate-to-severe AD in patients 12 years and older in the United States and in Europe. It is a fully human monoclonal antibody against IL-4Rα that blocks both IL-4 and IL-13 signalling. In randomized controlled trials of up to 52 weeks, treatment with dupilumab as monotherapy or in combination with TCS improved multiple measures of AD signs and symptoms as well as health-related quality of life.[161–165] Data from registries and real-world case series showed comparable response rates.[166–168]

The safety profile of dupilumab is favourable with conjunctivitis and blepharitis being the most frequent side-effect observed in up to 22.1% of dupilumab users in clinical trials[169] and up to 38.2% in real-world settings.[167] Most conjunctivitis cases are transitory and can be successfully managed without dupilumab withdrawal.[169] Treatment options for dupilumab-associated conjunctivitis include artificial tears for mild cases, topical corticosteroid fluorometholone 0.1% eye drops, topical calcineurin inhibitor ointment applied to the eye lids for moderate, and eye drops or ointments containing cyclosporine or tacrolimus for severe forms.[170–172] In addition, a paradoxical head and neck erythema, also known as red face syndrome, may develop with prolonged use of dupilumab, but can be treated with topical antimycotic or anti-inflammatory preparations.[173,174] Noteworthy and in contrast to many other biologics, there appears to be no need for laboratory monitoring.[175] Dupilumab should be combined with daily emollients and may be combined with topical anti-inflammatory drugs as needed.[84] Conventional systemic immunosuppressants may be continued in the first weeks after initiation of dupilumab treatment until the full clinical outcome is reached.[166] Dupilumab is currently approved for adults and children aged 12 years and above. Phase III data on children aged 6 years and above are available, and a timely approval for this age group is expected. The approval of dupilumab for certain forms of severe asthma and severe chronic rhinosinusitis with nasal polyposis by the EMA may also be relevant when choosing a drug.

The ETFAD recommends dupilumab for the treatment of patients aged 12 years or over with moderate-to-severe atopic dermatitis, who are candidates for systemic therapy.

Biologics in clinical trials

Many other biologics, which interfere with different cytokines and signalling pathways, are currently being tested in phase 2 and phase 3 trials, e.g. tralokinumab (anti-IL-13), fezakinumab (anti-IL-22), etokimab (anti-IL-33), nemolizumab (anti-IL-31Rα) and tezepelumab (anti-TSLP),[141] and may become available in the next years.

Recently published phase 2 studies demonstrated that monoclonal antibodies blocking IL-13 (lebrikizumab, tralokinumab) are effective in patients with moderate-to-severe AD.[176,177] By applying fezakinumab, an anti-IL-22 antibody, a significant decline of disease severity scores (SCORAD, affected body surface area and investigator global assessment) could be achieved and a pathogenic role for IL-22 in severe AD was demonstrated.[178] Two-phase 2 studies with nemolizumab, the anti-IL-31 receptor antibody, showed a large reduction in pruritus and in parallel improvement of clinical signs of AD underlining the role of the itch-scratch cycle.[179,180] The improvement of pruritus and dermatitis scores from baseline is maintained or may even increase upon long-term treatment (up to 64 weeks) with nemolizumab.[181] The difficult-to-treat subgroup of patients with prurigoform AD may profit especially well from nemolizumab.[182] A proof-of-concept study reported a rapid and sustained effect of a single administration of etokimab, an anti-IL-33 monoclonal antibody, in patients with AD.[183]

The ETFAD recommends checking on a regular basis all upcoming information in this field, as the licensing of new drugs for the treatment of AD is likely.

Antibacterial and antimycotic therapy

AD patients are more susceptible to secondary skin infections which tend to generalize, especially with *S. aureus*, Malassezia furfur and herpes simplex virus.[184,185] The inflammatory micro-milieu initiated by thymic stromal lymphopoietin (TSLP), IL-4 and IL-13 downregulates important cutaneous antimicrobial peptides such as cathelicidin LL-37, dermcidin and human β-defensins HBD-1, HBD-2 and HBD-3.[184,186] The understanding of colonization and

infection in AD has largely increased by detailed investigation of the human microbiome. A *S.aureus*-driven loss of diversity of the cutaneous microbiome is significantly associated with flares of AD, but not if patients have followed a proactive therapy regimen before the flare.[187] In up to 90% of AD patients, even non-lesional skin is extensively colonized by *S. aureus*. Many commensal bacteria, such as *S. epidermidis,* produce inhibitors that decrease *S. aureus* growth.[188] Strains of *S. aureus* found on AD patient's skin are different from strains isolated from the nasal carriers in normal population.[189]

S. aureus is a major trigger of AD, as inflammation is triggered through the release of toxins with superantigenic properties. These superantigens enhance T-cell activation in the skin, and also increase the expression of IL-31, leading to pruritus.[190] 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 the expression of alternative glucocorticoid receptors that do not bind topical corticosteroids, which leads to steroid resistance.[191] Biofilm formation by AD-associated staphylococci may play a major role in the occlusion of sweat ducts leading to inflammation and pruritus.[192]

Antibacterial therapy

Regular cleansing of the skin with syndets, topical antiseptics and antibiotics, systemic antibiotics and functional textiles have been used to reduce *S. aureus* on AD patients' skin. In clinical practice, a selection must be done based on clinical aspects, as all of these measures have strengths and weaknesses. Most interventions aim at reducing the burden of *S. aureus*.

Newly developed emollients include active compounds that influence the microbiome of AD with bacterial lysates from *Aquaphilus dolomiae* or *Vitreoscilla filiformis* species.[193] These are usually well-tolerated and improve the epidermal barrier as an added value, but the antibacterial effect against *S. aureus* seems low compared with antiseptics or systemic antibiotics. Physicians should not forget that a proper, well-conducted anti-inflammatory therapy with TCI or TCS will also reduce the colonization with *S. aureus*.

Both topical antiseptics and topical antibiotics may reduce *S. aureus* and other potentially helpful bacteria from the skin, but bacterial resistance and contact allergy are an issue. There is no clear benefit of antiseptic bath additives, antiseptic soaps or other antimicrobial agents added to topical therapies in non-infected atopic dermatitis, as evidenced in a large systematic review of 26 studies including 1229 participants.[194] Nevertheless, if there is no response to topical TCS or TCI, or evident infection, the use of topical antiseptics may be considered. These are preferred over topical antibiotics, as the development of bacterial resistance is less likely. A more recent systematic review published in 2017 confirmed these results.[195]

Sodium hypochlorite 0.005% has antiseptic properties and enhances in addition epidermal thickness and proliferation.[196] Its intermittent use showed a significant decrease in AD severity.[197] The addition of 100 mL of normal sodium hypochlorite household bleach (most come as 5% solution) to a full bath of 100-L tap water is the usual procedure. Potassium permanganate, which is the classical antiseptic substance, may stain bathtubs and patients and is difficult to get in some countries.

Impetigo is easily diagnosed by the yellow crusts and can be treated with fusidic acid, topical mupirocin or topical retapamulin for 5 days.[198] The high rate of *S. aureus* resistance against fusidic acid in Europe compared with the United States reflects the more frequent use in Europe.[199]

Systemic antibiotics should only be used in case of apparent and extensive bacterial superinfection. Based on the current resistance spectra, cephalexin or another first-generation cephalosporin can be recommended.[200] Children with AD seem to have a much lower rate of community-acquired methicillin-resistant *S. aureus* infection compared with the general paediatric population.[201]

Hidden sources of bacteria are cream and ointment containers, of which up to 53% are contaminated by bacteria, in 25% by *S. aureus*. Thus, the following recommendations seem to be useful [202]: (i) keep open moisturizers in refrigerator; (ii) use pumps or pour bottles rather than jars; (iii) avoid direct contact with hands and decant; and (iv) avoid sharing personal hygiene items.

The ETFAD recommends considering topical antiseptic drugs and antiseptic baths in addition to an adequate anti-inflammatory treatment with TCS and TCI, if clinical signs of strong colonization or bacterial superinfection are present. A long-term application of topical antibiotics is not recommended due to the risk of increasing resistances and sensitizations. A short course of systemic antibiotics, such as a 1st-generation cephalosporin, may be considered in AD patients with widespread and severe *S. aureus* infection.

Antimicrobial textiles

Various functional textiles with antimicrobial properties and different qualities have been on the market for years and have been worn for either 24 h or overnight only. Silver-coated textiles are assumed to release low amounts of silver ions to the skin, where a moderate antiseptic effect is observed. The physical stability and resistance to repeated washings of these different textiles are quite heterogeneous.[203] AEGIS-coated silk textiles are another product line in this niche.

Silver-impregnated textiles have shown significant antimicrobial activity, as well as improvement of localized SCORAD in an unblinded, side-to-side controlled clinical trial.[204] In patients with uninfected AD, the use of silver-impregnated textile compared with cotton underwear did not reduce AD severity.[205–207] 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 AD manifestations, as they decrease skin colonization by *S. aureus* and reduce itch.[208] Some of these newer options are still under investigation regarding the safety of silver-coated textiles in infants and toddlers. AEGIS-coated silk textiles did not show clinical benefit in a well-controlled, multicentre clinical trial.[209]

More recent studies evaluated these antimicrobial textiles in real life. Some silver-impregnated textiles lose their antimicrobial activity after 70 laundry cycles, whereas some others remain intact and still effective after 150 laundry cycles.[203] A second study described that this kind of textiles was unable to modify skin colonization with *S. aureus* under practical wear conditions (dry textiles), but the effectiveness could be enhanced by wetting the textiles. The authors found also that some moisturizing cream remains on the fibres after laundry.[210] In conclusion, efficacy and stability have been demonstrated for some silver products, and all silk and silver products are considered safe.

The ETFAD recommends considering high-quality silver garments to AD patients tending to strong colonization or infection with *S. aureus*.

Antiviral therapy

Viral infections with herpes simplex virus, varicella zoster virus, molluscum contagiosum virus, smallpox virus and Coxsackie virus occur more frequently in AD patients than in healthy individuals, with a tendency to cause disseminated, widespread disease.[185]

Eczema herpeticum (EH), a disseminated *herpes simplex virus* (HSV) infection, is a potentially lethal complication of AD that requires immediate medical action. Patients, mostly children, present with disseminated, distinctly monomorphic vesicles, fever and lymphadenopathy. Complications such as keratoconjunctivitis, meningitis and encephalitis are rarely encountered.[100] A depletion of plasmacytoid dendritic cells, a failure of upregulation of the antimicrobial peptide LL-37 and an unmasking of the entry receptor nectin-1 by lesional spongiosis are considered relevant for the pathogenesis of EH.[100,211] IL-4 and IL-13 suppress keratinocyte expression of the antimicrobial peptide LL-37, which has a potent antiviral activity against HSV.[212] Some genetic variants of transcription factor STAT6, which regulates IL-4, are associated with EH in AD patients.[213] Predisposing factors of EH are early onset of AD, severe or untreated forms of AD, filaggrin deficiency, high total serum IgE level, elevated allergen-specific IgE and peripheral eosinophilia.[185,214] Almost all EH patients are of the extrinsic AD subtype [100], and Th2 polarization of HSV-1 specific T cells has been shown in EH patients.[215] Pretreatment with TCS does not seem to imply an increased risk of developing EH, whereas TCI may do so and should be paused for some weeks.[216] Mainstay of EH therapy is a systemic treatment with aciclovir or valaciclovir.[213] Treatment should be started immediately once the diagnosis is clinically suspected.[3] Patients with AD have a fourfold increased risk of developing ocular HSV infections. For AD patients with a history of HSV keratitis, a long-term oral antiviral prophylaxis may be advisable because of the potential vision loss risk due to scarring cornea.[217] The rate of localized HSV infections in AD patients treated with dupilumab is higher compared with placebo, but lower for EH and varicellazoster virus infection.[218]

Varicellazoster virus (VZV)infection in an immunocompetent child is usually a mild, self-limited disease. This infection is known to facilitate secondary local or systemic bacterial infection, which is cause for particular concern in AD children. The safety and efficacy of VZV vaccination in AD children are well-established.[219] Moreover, in children with AD, common childhood immunization in the first year is not associated with an increased risk of more severe AD or allergic sensitization; also, immune response to VZV vaccine is comparable to healthy children.[220] Therefore, parents of atopic children should be encouraged to follow their local vaccination plan including VZV vaccination.

Molluscum contagiosum virus (MCV) infection is in general benign and self-limited, but dissemination is frequent in AD patients, and therefore, treatment is recommended. MCV infection seems to be a trigger for disease onset or flare of AD in children with a positive family history of AD.[221] A large variety of topical treatments have been reported such as cantharidin, potassium hydroxide, tretinoin cream, topical cidofovir and others.[222] Physical therapies including cryotherapy and curettage are also effective, but not always well-tolerated in paediatric patients.[185] Topical treatment of AD with TCS and TCI may be continued during MCV infection.

Eczema vaccinatum (EV) is a complication of smallpox vaccination known to occur in AD patients. The vaccinia virus disseminates and causes an extensive rash and severe systemic illness with a mortality rate estimate at 5%–40%.[223] Therefore, smallpox vaccination is contraindicated in patients with a history of or currently active AD.[224] The existence of an attenuated vaccine and three antiviral drugs, in addition to vaccinia immunoglobulin, provides means of preventing or treating EV.[225,226] Should a smallpox outbreak necessitate an emergency mass vaccination, the choice of vaccination strategies has to be determined by policymakers.

Eczema coxsackium (EC) is a disseminated form of Coxsackievirus infection mostly occurring in children with active AD lesions. The Coxsackievirus 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).[227] Symptomatic treatment includes use of TCS and wet-wrap therapy.[228,229]

The ETFAD recommends following all regional vaccination programmes including the VZV vaccination as recommended.

Parents of atopic children should be encouraged to fully immunize their children. The denial of vaccination because of diagnosed AD is a common misconception possibly leading to fatal consequences (see chapter: general measures). Eczema herpeticum should be treated upon suspicion immediately using systemic antiviral therapy, such as systemic acyclovir or valaciclovir.

Antifungal therapy

Malassezia spp. is a commensal on healthy human skin, but is attributed a pathogenic role in AD, as it may interact with the local skin immune response and barrier function. There is evidence for a molecular mimicry between fungal and human superoxide dismutase and thioredoxin proteins, which may contribute to the pathogenesis of AD.[230]

Several randomized, placebo-controlled trials investigated the benefit of topical or systemic antifungal treatment for AD patients.[231,232] 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 AD. It seems, for example, that antifungal therapy shows beneficial effects in patients with a head–neck-type distributed AD and detectable IgE-mediated sensitization against Malassezia.[233] Sensitization against this skin-colonizing yeast correlates with disease activity.[234] The most common class of antifungal drugs prescribed for AD patients are azoles such as ketoconazole and itraconazole, which have also some anti-inflammatory properties.[232]

The ETFAD recommends considering antifungal treatment with either topical ketoconazole or ciclopirox olamine for patients suffering from atopic head–neck dermatitis, and particularly for those with known IgE-sensitization to *Malassezia* spp.

Complementary medicine for the treatment of AD

Complementary medicine describes a wide variety of healthcare practices used alongside standard medical treatment. Examples of complementary medicine include alternative health approaches such as traditional Chinese medicine, homeopathy and naturopathy.[5] Many patients with AD, in some studies over 50%, have used complementary medicine for primary or adjunctive treatment.[235,236]

There are an increasing number of trials studying complementary medicine for the treatment of adults and children with AD.[237] The most frequently used modalities are herbal medicine, vitamins, Ayurveda, naturopathy, homeopathy and traditional healing.[237] Most studies are small and with low methodologic quality.[5] Many studies do not report adverse effects in a proper way and safety often remains unclear due to insufficient reporting.[237] It should be noted that kidney failure and liver damage have been reported in association with traditional Chinese medicine.[238] A Cochrane review published in 2013 included 28 randomized controlled trials comparing Chinese herbal medicine (CHM) to placebo. The authors could not find conclusive evidence that CHM taken orally or applied topically to the skin could reduce the severity of eczema in children or adults.[239] Another Cochrane review showed that oral borage oil and evening primrose oil lack effect in eczema.[240] The effect of n-3 (or omega 3) long-chain polyunsaturated fatty acid supplementation in pregnant or breastfeeding women on allergy outcomes in their children was assessed. For any allergy, no clear differences were seen in children between 12 and 36 months, nor beyond 36 months of age.[241]

No evidence-based recommendations can be made from the available literature.[238] There is a great need for higher-quality studies to guide patients as well as clinicians. Well-designed randomized trials are necessary to confirm a beneficial effect and to establish safe use. Future studies should be designed as double-blinded, placebo-controlled trials, with sufficient power and reported according to the CONSORT (Consolidated Standards for Reporting Trials) statement.[242,243] It is also important that the core outcome set and core outcome instruments are chosen in accordance with the harmonizing outcome measures for eczema.[244,245]

The ETFD does not recommend complementary medicine for the treatment of AD.

Vitamins and probiotics

The role of vitamin D and the vitamin D receptor (VDR) in AD has been studied in three single centre randomized placebo-controlled studies including a total of 142 patients. One study found a significant clinical effect, but concomitant routine treatment was allowed and not registered.[246] Better-designed studies did not find a beneficial effect of vitamin D supplementation on AD manifestations.[247-249] A recent systematic review, focused on the effects of vitamin D levels and supplementation in children with AD, confirmed a link between serum vitamin D levels and AD severity, but only weak evidence was found supporting improvement of AD with vitamin D supplementation.[250] Hence, supplementation of vitamin D is useful neither for treatment nor for prevention of AD.[251]

Treatment regimens with probiotics aim to modulate the microflora in the gut in order to stimulate the immune response towards an allergy-protecting, T-helper 1-biased immune reaction.[252] There are several studies on the therapeutic effects of probiotics, but recent meta-analyses on the effect of probiotics in pregnant women[253] and in children[254] do not demonstrate convincing effects of this treatment modality compared with earlier meta-analyses.[255,256] In a recent Cochrane review assessing the effects of probiotics for treating patients of all ages, the authors concluded that compared to no probiotics, currently available probiotic strains probably make little or no difference in improving patient-rated eczema symptoms.[257]

The ETFAD does not recommend vitamin D or probiotics for the treatment of AD.

Specific considerations for children

The anatomical and pathophysiological peculiarities of children, such as an incomplete skin barrier, a higher surface-to-body weight ratio, a less experienced immune system – together with the fact that many drugs effective for AD are not licensed for them – result in special considerations and treatment rules for young AD patients, especially for those aged 2 years and younger. The larger surface area-to-body weight ratio in infants can result in an up to 2.7 times higher systemic exposure which implies a greater risk of intoxication.

The clinical presentation of infantile AD shows different predilection sites and a tendency towards exudative lesions, especially on the cheeks. Establishing a diagnosis of AD may be difficult in this age group, because the classic diagnostic criteria cannot be applied. In early-onset severe AD (<3 months), some primary immunodeficiency syndromes such as Omen syndrome, selective IgA deficiency, hyper-IgE syndromes and Wiskott–Aldrich syndrome, some genetic disorders with an impaired barrier function such as Comel–Netherton syndrome and peeling skin syndrome, and some inherited metabolic diseases such as biotin deficiency or phenylketonuria may be differential diagnoses.[258]

Stress and conflicts in the family may trigger AD in young children. Flares are associated with contact to non-familiar pets, swimming in chlorinated pools and direct skin exposure to wool (except superfine merino wool[259]) and nylon textiles.[260] Prevention and early recognition of atopic respiratory diseases and food allergies are important during childhood and adolescence. In children, food allergies triggering an exacerbation are more common than in adults. For small children, cow's milk protein and hen egg are the most common relevant allergens. In adolescents, pollen-associated food allergens are more important. Food allergies in young children are often transient, making follow-up investigations necessary to assess the development of tolerance.[261] Attention-deficit hyperactivity disorder (ADHD) and autistic spectrum disorder (ASD) have been identified as possible comorbidities of AD.[262]

The principles of topical treatment are the same as in adults, but are adapted with respect to an increased absorption and altered surface-to-body weight ratio. The use of weaker TCS (classes 1 and 2) in small children is common practice of many dermatologists and paediatricians. Especially critical areas in infants are the diaper area, the face and the scalp. An increased use of TCI to spare TCS is widely advocated due to the ever-increasing experience and long-term safety data with the substance class.[32,93] The off-label use of both TCIs in children under 2 years of age has been considered appropriate in the latest European Guideline on Treatment of AD, based on good-quality long-term safety data recently published for TCI in infants.[4,95,96]

Hypoallergenic topical preparations should be prescribed in children with AD, as these have a significantly higher risk of developing contact allergy to components of skincare products than children with healthy skin.[263] Glycerol as a moisturizer in emollients is better tolerated than urea in children under 5 years of age. Urea is a good emollient ingredient if used at 5% or less. It is not only a humectant, but also induces the expression of NMF ingredients in the skin. Sophisticated emollients may contain urea, glycerol and ceramides. There are good data from the AD flare prevention trials on tolerability. Topical drugs leading to severe side-effects include salicylic acid and disinfectants containing alcohol.[264]

Systemic treatment for children is administered on an individual patient basis in severe cases only, and there is no consented standard treatment for the substances or the duration. The most commonly used anti-inflammatory drug in Europe was CyA, followed by SCS and AZA.[265] Recently, low-dose MTX was shown to have a good safety profile in children,[266,267] even for long-term treatment,[147] and an effectiveness comparable to CyA.[268] Difficult-to-treat nummular forms of AD in children have also responded to MTX treatment.[269] Most systemic treatment of children and adolescents is expected to shift to dupilumab, once the expected licence for children is obtained.

Nocturnal pruritus is a common problem in medium-to-severe AD. A recent Cochrane Review concluded that there is no consistent evidence for the effectiveness of oral H1 antihistamines.[133] Sedating H1 antihistamines may be tried for a short period in acute exacerbations, when sleep disturbances persist despite TCS and emollient use,[270] but long-term use is not recommended.

Vaccinations, including those against measles, are generally safe in hen's egg-allergic AD patients,[271] the only restriction being the quality of skincare to avoid superinfection at injection sites. Though smallpox vaccination was contraindicated in children with AD to avoid eczema vaccinatum,[224] vaccinations against varicella are recommended to avoid severe cutaneous viral infections.[4]

Therapeutic parent and child education ('eczema school') is an integrated part of AD management and especially valuable for reducing AD symptoms.[77,272] Written treatment instructions, such as the 'Personalized Written Action Plan for Atopics', may be very useful.[273] For treatment adherence, it is important to establish a good relationship with the parents and consider the burden of disease they carry.[21]

The ETFAD recommends that for children, especially below 2 years of age, increased attention should be paid to the safety, tolerability and hypoallergenic properties of all components of topicals for the treatment and skincare of AD. Systemic treatment should be initiated by experienced specialists only.

Specific considerations for adolescents

Adolescents are neither children nor adults, and to optimize the management of their AD, some specific elements should be considered. Adolescent patients develop more autonomy and must

learn to take care of their chronic disease in an independent way. Adolescent becoming the actors of their own skincare must be addressed directly and is possible without their parent's presence. Specific aspects have to be discussed such as sleep habits, daily skin treatment routine, management of comorbidities and aspects of health-related quality of life such as peer relationships, intimacy, sexuality and body image.[274]

Evaluation of daily skincare is essential. It seems that particularly adolescents either do not bath or shower much or do so with an excessive duration, which can aggravate AD and increases the risk of skin infection.[36] Adherence to a daily treatment routine is very difficult in this age group. The risk of striae from TCS absorption during puberty is high, and wet-wrapping therapy with TCS should be used as a short-term therapy and with caution only.[275] Therefore, adolescents need clear advice on how to use their TCS in combination with emollients[276] and specific age-related therapeutic patient educational programmes should be discussed as effective long-term management strategies of the disease.[77]

Teenagers with AD are more prone to specific types of allergic contact dermatitis.[277] The most frequent allergen is nickel. It could be present not only in belt buckles, button flies and jewelleries, but also in cell phone covers and electronic devices.[278]

Adolescents with AD are more likely to experience psychological challenges compared with their healthy peers. Children of all age groups with AD had a significant increased risk of total mental disorders compared with those without AD.[279] Particularly in late adolescence, AD is associated with suicidal ideation and mental health problems.[280] Adolescents with AD have a higher risk of the developing a depressive or anxiety disorder later in life.[281] The relationship between suffering from AD and mental disorders may be reciprocal.[282]

Most adolescents with AD have experienced social exclusion or were bullied during childhood due to their skin disease, which negatively affects self-perception and self-esteem.[283] Older children or adolescents reportedly have fewer friends, participate in less social events or sports teams.[284] The way an adolescent feels about his body image is closely linked to self-esteem and difficulties related to body image are common in adolescence. Therefore, AD can also have a heavy impact on the capacity for intimacy and sexual life, as it implicates appearance and personal relationship. As quality of life correlates with the severity of AD and psychological or social impairment, a holistic approach could include psychological assessment, psychotherapy, behavioural therapy and coping strategies.[285,286]

AD can have an impact on school performance and on future professional life. Developing AD later during childhood or adolescence could lead to a higher risk of having persistent AD in adulthood, which can have an impact on the productivity at work.[287] However, having AD during adolescence does not seem to negatively impact academic performance.[288] Therefore, career choices should be discussed with adolescent patients.

The ETFAD acknowledges the special requirements of adolescent AD patients and recommends discussing them actively.

Occupational aspects

AD patients are running a significant risk of developing occupational contact dermatitis. Atopy amplifies the effects of irritant and allergen exposure in hairdressers, cleaners, metalworkers, mechanics and nurses, where hand eczema is a very common disease.[76] The skin of patients with AD is more reactive to skin irritants, which in turn increases their risk of developing occupational irritant and allergic contact dermatitis on the hands.[289] Accordingly, patients with AD have three- to fourfold increased risk of occupational hand eczema.[290]

Occupations in which exposure to skin irritants such as water, detergent, machine oil and gloves is common can therefore be challenging for individuals with a history of AD. Physicians should inform their patients with AD about these risks and provide careful guidance about prophylactic skin protection. The risk of occupational hand eczema is generally higher for hairdressers, mechanics, bakers, chefs, nurses and painters. Adolescents with AD should consider this when choosing their profession.

The ETFAD recommends that preventive strategies should be developed and optimized to reduce the incidence of occupational dermatitis in AD patients. Dermatologists should advise their AD patients early on occupational aspects of their disease and suitable career choices.

Psychosomatic aspects and therapeutic patient education

Psychosomatic aspects of AD

Psychosomatic treatment could complement topical and systemic therapy and should be divided into unimodal and multimodal psychological itch treatments.[291] Depending on the factors involved, a unimodal (e.g. progressive muscular relaxation or autogenic training) [292] or multimodal psychological approach is recommended.[291]

The vicious itch-scratch cycle has to be considered when a patient is treated for pruritus. The psychosomatic approach recognizes the itch patient with regard to coping behaviour and possible stress attempts as cause or provocation factor in chronic itch. Parents' behaviour and skincare management may influence the severity of the disease.[293] In addition to causal and symptomatic therapy, behavioural therapy to avoid scratching should be considered, e.g. conscious suppression of the reflex by intense concentration, distraction or alternative scratching techniques such as habit reversal.[294] This is very important in patients with AD and especially in those who might show an unconscious automatic scratching behaviour.

Adjuvant psychosocial programmes focused on itch are most effective in AD, and many randomized controlled trials have

been published in the recent years.[295–306] Such programmes include strategies for breaking the vicious circle of itching and scratching, relaxation and stress management techniques as well as strategies for dealing with relapses. More than 10 randomized controlled studies [296,307,308] and a Cochrane review about psychological interventions showed slightly beneficial effects.[309] Overall, counselling of AD patients is cost-effective.[307,310]

A similar educational programme was developed for patients with chronic pruritus.[311,312] It is currently established for in-patient hospital treatment of patients with pruritic dermatoses using behavioural therapy in the context of an integrated psychosomatic treatment.[300,313] Habit-reversal techniques are especially effective as an additional management for itch in AD patients.[314] Relaxation techniques are easy to practice and are demonstrated in specific age-related therapeutic patient educational programmes.[22,77] In patients with coexisting depression, psychotherapy in combination with psychotropic medication can be helpful even to treat pruritus of different aetiology.[315] Most publications on psychotherapeutic and psychopharmacologic interventions, however, refer to small groups or single case reports.[316,317] Internet-delivered (eHealth) self-management was investigated in recent years mostly with cognitive behavioural interventions.[306,318] Results demonstrate similar effects such as face-to-face psychotherapy.[319] Studies involving dermatologic patients are promising.[320]

The ETFAD recommends multimodal education programmes to increase coping behaviour in patients suffering from AD. Relaxation techniques and habit-reversal techniques for AD patients are also useful as a complementary treatment for managing the disease.

Therapeutic patient education (eczema school)

Poor adherence to prescribed treatment is frequent and leads to therapeutic failure.[21] There is a significant and urgent need for physicians to ensure that patients with AD are educated and confident in using medication as prescribed to gain disease control. This education is designed to train patients or parents of children suffering from AD in the skills of self-management or adapting treatment to their particular chronic disease and in coping processes and skills. Educational intervention will help for the management of difficult-to-treat atopic patients. Standardized interdisciplinary programmes involving dermatologists, paediatricians, psychologists, psychosomatic counsellors and dietary counselling have been demonstrated to improve subjective and objective symptoms, optimize medication use in patients and result in a significant gain in quality of life.[22,77] Support materials for healthcare professionals and for parents can be found on >www.fondation-dermatite-atopique.org<.

The ETFAD recommends participation in a therapeutic education programme for AD to all patients with moderate and severe AD.

Optimizing patient adherence

Poor treatment adherence is one of the most common causes of treatment failure. Hence, the ability to distinguish reliably between non-adherence and non-response, and mastering the active use of adherence-improving strategies are most important for treating AD patients successfully.[21] Factors influencing treatment adherence include patient characteristics and beliefs, treatment efficacy and duration, administration routes and disease chronicity. Moreover, the quality of the physician–patient relationship including physician-time available for the patient as well as 'shared decision-making' plays an important role.[21] Strategies to increase treatment adherence range from handing out written action plans, minimizing treatment costs, thoughtfully scheduled follow-up visits and reminder programmes to simplifying prescriptions or educational interventions.[21,273] A recent systematic review summarizes the evidence and recommendations.[21]

Outlook and future perspectives

The simultaneous emergence of many new topical and systemic drugs for the treatment of AD in clinical trials, and the perspective for some licensed systemic drugs even for childhood AD in the near future have considerably changed the field of AD management. A combination of limited resources and increased digitalization will emphasize the quality of care as an important issue also for the management of AD.[321] The impact of the COVID-19 pandemic on the availability of health care resources for AD patients cannot be predicted, even if an interaction with systemic medication seems low.[322] A carefully selected topical emollient therapy, allergen avoidance based on a thoroughly taken history and allergy testing, and a wise selection of topical anti-inflammatory therapy will still be needed in the future. Therapeutic patient education for children, their caregivers and adult patients suffering from AD supports and assures medical treatment, as it is safe and cost-effective. Moreover, digitalization of many aspects of patient care and artificial intelligence will for sure enter the field of AD management. Many new aspects of evidence-based care for AD patients will further change our daily practice in the next 5 years. New patient leaflets replacing the current ETFAD patient information sheet available at < https://www.eadv.org/patient-corner/leaflets>, and additional online information will witness these changes in due time.

Acknowledgement

The authors thank Quirine Eijkenboom, BSc, Munich, for her support during the formation of the manuscript. Open access funding enabled and organized by Projekt DEAL.

References

1 Darsow U, Lubbe J, Taieb A *et al*. Position paper on diagnosis and treatment of atopic dermatitis. *J Eur Acad Dermatol Venereol* 2005; **19**: 286–295.
2 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.

3 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.
4 Wollenberg A, Barbarot S, Bieber T *et al*. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. *J Eur Acad Dermatol Venereol* 2018; **32**: 657–682.
5 Wollenberg A, Barbarot S, Bieber T *et al*. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. *J Eur Acad Dermatol Venereol* 2018; **32**: 850–878.
6 Vestergaard C, Wollenberg A, Barbarot S *et al*. European task force on atopic dermatitis position paper: treatment of parental atopic dermatitis during preconception, pregnancy and lactation period. *J Eur Acad Dermatol Venereol* 2019; **33**: 1644–1659.
7 Werfel T, Allam JP, Biedermann T *et al*. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol* 2016; **138**: 336–349.
8 Mortz CG, Andersen KE, Dellgren C, Barington T, Bindslev-Jensen C. Atopic dermatitis from adolescence to adulthood in the TOACS cohort: prevalence, persistence and comorbidities. *Allergy* 2015; **70**: 836–845.
9 Ring J, Przybilla B, Ruzicka T. Handbook of Atopic Eczema, 2nd edn. Springer, Berlin, 2005.
10 Schmid-Grendelmeier P, Simon D, Simon HU, Akdis CA, Wüthrich B. Epidemiology, clinical features, and immunology of the "intrinsic" (non-IgE-mediated) type of atopic dermatitis (constitutional dermatitis). *Allergy* 2001; **56**: 841–849.
11 Schultz-Larsen F. Atopic dermatitis. Etiological studies based on a twin population. Laegeforeningens, Kopenhagen, 1985.
12 Weidinger S, Illig T, Baurecht H *et al*. Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. *J Allergy Clin Immunol* 2006; **118**: 214–219.
13 Ezzedine K, Droitcourt C, Ged C *et al*. Usefulness of a global clinical ichthyosis vulgaris scoring system for predicting common FLG null mutations in an adult caucasian population. *Br J Dermatol* 2012; **167**: 1165–1169.
14 Proksch E, Dahnhardt D, Dahnhardt-Pfeiffer S, Folster-Holst R. Epidermale Barrierestorung bei Dermatosen. *Hautarzt.* 2016; **67**: 907–921.
15 Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Stockh) Suppl* 1980; **92**: 44–47.
16 Williams HC. Established corticosteroid creams should be applied only once daily in patients with atopic eczema. *BMJ* 2007; **334**: 1272.
17 Ariens LFM, van Nimwegen KJM, Shams M *et al*. Economic burden of adult patients with moderate to severe atopic dermatitis indicated for systemic treatment. *Acta Derm Venereol* 2019; **99**: 762–768.
18 Eckert L, Gupta S, Gadkari A, Mahajan P, Gelfand JM. Burden of illness in adults with atopic dermatitis: analysis of National Health and Wellness Survey data from France, Germany, Italy, Spain, and the United Kingdom. *J Am Acad Dermatol* 2019; **81**: 187–195.
19 Dalgard FJ, Gieler U, Tomas-Aragones L *et al*. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. *J Invest Dermatol* 2015; **135**: 984–991.
20 Balieva F, Kupfer J, Lien L *et al*. The burden of common skin diseases assessed with the EQ5D: a European multicentre study in 13 countries. *Br J Dermatol* 2017; **176**: 1170–1178.
21 Eicher L, Knop M, Aszodi N, Senner S, French LE, Wollenberg A. A systematic review of factors influencing treatment adherence in chronic inflammatory skin disease - strategies for optimizing treatment outcome. *J Eur Acad Dermatol Venereol* 2019; **33**: 2253–2263.
22 Heratizadeh A, Werfel T, Wollenberg A *et al*. Effects of structured patient education in adults with atopic dermatitis: Multicenter randomized controlled trial. *J Allergy Clin Immunol* 2017; **140**: 845–853.e3.
23 Wollenberg A, Bieber T. Proactive therapy of atopic dermatitis–an emerging concept. *Allergy* 2009; **64**: 276–278.
24 Barbarot S, Rogers NK, Abuabara K *et al*. Strategies used for measuring long-term control in atopic dermatitis trials: a systematic review. *J Am Acad Dermatol* 2016; **75**: 1038–1044.
25 European Task Force on Atopic Dermatitis. Severity Scoring of Atopic Dermatitis: The SCORAD Index. *Dermatology* 1993; **186**: 23–31.
26 Kunz B, Oranje AP, Labrèze L, Stalder JF, Ring J, Taïeb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1997; **195**: 10–19.
27 Langan SM, Schmitt J, Williams HC, Smith S, Thomas KS. How are eczema 'flares' defined? A systematic review and recommendation for future studies. *Br J Dermatol* 2014; **170**: 548–556.
28 Stalder JF, Barbarot S, Wollenberg A *et al*. Patient-Oriented SCORAD (PO-SCORAD): a new self-assessment scale in atopic dermatitis validated in Europe. *Allergy* 2011; **66**: 1114–1121.
29 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.
30 Taïeb A. Dermatite atopique: définition, épidémiologie, histoire naturelle, scores de gravité. *Ann Dermatol Venereol* 2005; **132**: 1535–1543.
31 Schmitt J, von Kobyletzki L, Svensson A, Apfelbacher C. Efficacy and tolerability of proactive treatment with topical corticosteroids and calcineurin inhibitors for atopic eczema: systematic review and meta-analysis of randomized controlled trials. *Br J Dermatol* 2011; **164**: 415–428.
32 Wollenberg A, Ehmann LM. Long term treatment concepts and proactive therapy for atopic eczema. *Ann Dermatol* 2012; **24**: 253–260.
33 Howells L, Thomas KS, Sears AV *et al*. Defining and measuring 'eczema control': an international qualitative study to explore the views of those living with and treating atopic eczema. *J Eur Acad Dermatol Venereol* 2019; **33**: 1124–1132.
34 Gelmetti C, Wollenberg A. Atopic dermatitis - all you can do from the outside. *Br J Dermatol* 2014; **170**(Suppl 1): 19–24.
35 Koutroulis I, Petrova K, Kratimenos P, Gaughan J. Frequency of bathing in the management of atopic dermatitis: to bathe or not to bathe? *Clin Pediatr* 2014; **53**: 677–681.
36 Koutroulis I, Pyle T, Kopylov D, Little A, Gaughan J, Kratimenos P. The Association between bathing habits and severity of atopic dermatitis in children. *Clin Pediatr* 2015; **55**: 176–181.
37 Santer M, Ridd MJ, Francis NA *et al*. Emollient bath additives for the treatment of childhood eczema (BATHE): multicentre pragmatic parallel group randomised controlled trial of clinical and cost effectiveness. *BMJ* 2018; **361**: k1332.
38 Åkerström U, Reitamo S, Langeland T *et al*. Comparison of moisturizing creams for the prevention of atopic dermatitis relapse: a randomized double-blind controlled multicentre clinical trial. *Acta Derm Venereol* 2015; **95**: 587–592.
39 Draelos ZD, Feldman SR, Berman B *et al*. Tolerability of topical treatments for atopic dermatitis. *Dermatol Ther (Heidelb)* 2019; **9**: 71–102.
40 Elias PM, Wakefield JS, Man MQ. Moisturizers versus current and next-generation barrier repair therapy for the management of atopic dermatitis. *Skin Pharmacol Physiol* 2019; **32**: 1–7.
41 Dinkloh A, Worm M, Geier J, Schnuch A, Wollenberg A. Contact sensitization in patients with suspected cosmetic intolerance: results of the IVDK 2006–2011. *J Eur Acad Dermatol Venereol* 2015; **29**: 1071–1081.
42 Stander S, Augustin M, Roggenkamp D *et al*. Novel TRPM8 agonist cooling compound against chronic itch: results from a randomized, double-blind, controlled, pilot study in dry skin. *J Eur Acad Dermatol Venereol* 2017; **31**: 1064–1068.
43 Boussault P, Léauté-Labrèze C, Saubusse E *et al*. Oat sensitization in children with atopic dermatitis: prevalence, risks and associated factors. *Allergy* 2007; **62**: 1251–1256.
44 Wollenberg A, Folster-Holst R, Saint Aroman M, Sampogna F, Vestergaard C. Effects of a protein-free oat plantlet extract on microinflammation and skin barrier function in atopic dermatitis patients. *J Eur Acad Dermatol Venereol* 2018; **32**(Suppl 1): 1–15.

45 Macharia WM, Anabwani GM, Owili DM. Effects of skin contactants on evolution of atopic dermatitis in children: a case control study. *Trop Doct* 1991; **21**: 104–106.
46 Simpson EL, Berry TM, Brown PA, Hanifin JM. A pilot study of emollient therapy for the primary prevention of atopic dermatitis. *J Am Acad Dermatol* 2010; **63**: 587–593.
47 Simpson EL, Chalmers JR, Hanifin JM *et al*. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol* 2014; **134**: 818–823.
48 Horimukai K, Morita K, Narita M *et al*. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol* 2014; **134**: 824–830.e6.
49 Chalmers JR, Haines RH, Bradshaw LE *et al*. Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial. *Lancet* 2020; **395**: 962–972.
50 Skjerven HO, Rehbinder EM, Vettukattil R *et al*. Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial. *Lancet* 2020; **395**: 951–961.
51 Abrahamsson TR, Jakobsson HE, Andersson AF, Bjorksten B, Engstrand L, Jenmalm MC. Low diversity of the gut microbiota in infants with atopic eczema. *J Allergy Clin Immunol* 2012; **129**: 434–440, 440 e431–432.
52 Amalia N, Orchard D, Francis KL, King E. Systematic review and meta-analysis on the use of probiotic supplementation in pregnant mother, breastfeeding mother and infant for the prevention of atopic dermatitis in children. *Australas J Dermatol* 2020; **61**: e158–e173.
53 Osborn DA, Sinn JK. Prebiotics in infants for prevention of allergy. *Cochrane Database Syst Rev* 2013; **3**: CD006474.
54 Wassmann-Otto A, Heratizadeh A, Wichmann K, Werfel T. Birch pollen-related foods can cause late eczematous reactions in patients with atopic dermatitis. *Allergy* 2018; **73**: 2046–2054.
55 Hamann CR, Hamann D, Egeberg A, Johansen JD, Silverberg J, Thyssen JP. Association between atopic dermatitis and contact sensitization: a systematic review and meta-analysis. *J Am Acad Dermatol* 2017; **77**: 70–78.
56 Wassmann A, Werfel T. Atopic eczema and food allergy. *Chem Immunol Allergy* 2015; **101**: 181–190.
57 Bath-Hextall F, Delamere FM, Williams HC. Dietary exclusions for improving established atopic eczema in adults and children: systematic review. *Allergy* 2009; **64**: 258–264.
58 Sinagra JL, Bordignon V, Ferraro C *et al*. Unnecessary milk elimination diets in children with atopic dermatitis. *Pediatr Dermatol* 2007; **24**: 1–6.
59 Oranje A, Bruynzeel D, Stenveld H, Dieges P. Immediate- and delayed-type contact hypersensitivity in children older than 5 years with atopic dermatitis: a pilot study comparing different tests. *Pediatr Dermatol* 1994; **11**: 209–215.
60 Wollenberg A, Vogel S. Patch testing for noncontact dermatitis: the atopy patch test for food and inhalants. *Curr Allergy Asthma Rep* 2013; **13**: 539–544.
61 Muraro A, Werfel T, Hoffmann-Sommergruber K *et al*. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy* 2014; **69**: 1008–1025.
62 Schoos AM, Chawes BL, Folsgaard NV, Samandari N, Bonnelykke K, Bisgaard H. Disagreement between skin prick test and specific IgE in young children. *Allergy* 2015; **70**: 41–48.
63 Darsow U, Laifaoui J, Kerschenlohr K *et al*. The prevalence of positive reactions in the atopy patch test with aeroallergens and food allergens in subjects with atopic eczema: a European multicenter study. *Allergy* 2004; **59**: 1318–1325.
64 Turjanmaa K, Darsow U, Niggemann B, Rancé F, Vanto T, Werfel T. EAACI/GA2LEN Position Paper: present status of the atopy patch test – position paper of the section on dermatology and the section on pediatrics of the EAACI. *Allergy* 2006; **61**: 1377–1384.
65 Kerschenlohr K, Decard S, Darsow U, Ollert M, Wollenberg A. Clinical and immunologic reactivity to aeroallergens in "intrinsic" atopic dermatitis patients. *J Allergy Clin Immunol* 2003; **111**: 195–197.
66 Breuer K, Heratizadeh A, Wulf A *et al*. Late eczematous reactions to food in children with atopic dermatitis. *Clin Exp Allergy* 2004; **34**: 817–824.
67 Werfel T, Heratizadeh A, Niebuhr M *et al*. Exacerbation of atopic dermatitis on grass pollen exposure in an environmental challenge chamber. *J Allergy Clin Immunol* 2015; **136**: 96–103.e9.
68 Garritsen FM, ter Haar NM, Spuls PI. House dust mite reduction in the management of atopic dermatitis. A critically appraised topic. *Br J Dermatol* 2013; **168**: 688–691.
69 Herro EM, Matiz C, Sullivan K, Hamann C, Jacob SE. Frequency of contact allergens in pediatric patients with atopic dermatitis. *J Clin Aesthet Dermatol* 2011; **4**: 39–41.
70 Thyssen JP, McFadden JP, Kimber I. The multiple factors affecting the association between atopic dermatitis and contact sensitization. *Allergy* 2014; **69**: 28–36.
71 Paulsen E, Andersen KE. Sensitization patterns in compositae-allergic patients with current or past atopic dermatitis. *Contact Dermatitis* 2013; **68**: 277–285.
72 Isaksson M, Olhardt S, Rådehed J, Svensson A. Children with atopic dermatitis should always be patch-tested if they have hand or foot dermatitis. *Acta Derm Venereol* 2015; **95**: 583–586.
73 Uehara M, Sawai T. A longitudinal study of contact sensitivity in patients with atopic dermatitis. *Arch Dermatol* 1989; **125**: 366–368.
74 Arkwright PD, Motala C, Subramanian H *et al*. Management of difficult-to-treat atopic dermatitis. *J Allergy Clin Immunol Pract* 2013; **1**: 142–151.
75 Devillers AC, Oranje AP. Wet-wrap treatment in children with atopic dermatitis: a practical guideline. *Pediatr Dermatol* 2012; **29**: 24–27.
76 Janmohamed SR, Oranje AP, Devillers AC *et al*. The proactive wet-wrap method with diluted corticosteroids versus emollients in children with atopic dermatitis: a prospective, randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2014; **70**: 1076–1082.
77 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. *Br Med J* 2006; **332**: 933–938.
78 Wollenberg A, Schnopp C. Evolution of conventional therapy in atopic dermatitis. *Immunol Allergy Clin North Am* 2010; **30**: 351–368.
79 Wood Heickman LK, Davallow Ghajar L, Conaway M, Rogol AD. Evaluation of hypothalamic-pituitary-adrenal axis suppression following cutaneous use of topical corticosteroids in children: a meta-analysis. *Horm Res Paediatr* 2018; **89**: 389–396.
80 Eichenfield LF, Hanifin JM, Beck LA *et al*. Atopic dermatitis and asthma: parallels in the evolution of treatment. *Pediatrics* 2003; **111**: 608–616.
81 Fishbein AB, Mueller K, Lor J, Smith P, Paller AS, Kaat A. Systematic review and meta-analysis comparing topical corticosteroids with vehicle/moisturizer in childhood atopic dermatitis. *J Pediatr Nurs* 2019; **47**: 36–43.
82 Siegfried EC, Jaworski JC, Kaiser JD, Hebert AA. Systematic review of published trials: long-term safety of topical corticosteroids and topical calcineurin inhibitors in pediatric patients with atopic dermatitis. *BMC Pediatr* 2016; **16**: 75.
83 Kim JE, Shin JM, Ko JY, Ro YS. Importance of concomitant topical therapy in moderate-to-severe atopic dermatitis treated with cyclosporine. *Dermatol Ther* 2016; **29**: 120–125.
84 de Bruin-Weller M, Thaçi D, Smith C *et al*. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ). *Br J Dermatol* 2018; **178**: 1083–1101.

85 Lambrechts L, Gilissen L, Morren MA. Topical corticosteroid phobia among healthcare professionals using the TOPICOP score. *Acta Derm Venereol* 2019; **99**: 1004–1008.
86 Bornhövd E, Burgdorf WHC, Wollenberg A. Macrolactam immunomodulators for topical treatment of inflammatory skin diseases. *J Am Acad Dermatol* 2001; **45**: 736–743.
87 Ruzicka T, Bieber T, Schöpf E *et al*. A short-term trial of tacrolimus ointment for atopic dermatitis. *N Engl J Med* 1997; **337**: 816–821.
88 Van Leent EJ, Graber M, Thurston M, Wagenaar A, Spuls PI, Bos JD. Effectiveness of the ascomycin macrolactam SDZ ASM 981 in the topical treatment of atopic dermatitis. *Arch Dermatol* 1998; **134**: 805–809.
89 Reitamo S, Wollenberg A, Schopf E *et al*. Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. The European Tacrolimus Ointment Study Group. *Arch Dermatol* 2000; **136**: 999–1006.
90 Meurer M, Fartasch M, Albrecht G *et al*. Long-term efficacy and safety of pimecrolimus cream 1% in adults with moderate atopic dermatitis. *Dermatology* 2004; **208**: 365–372.
91 Reitamo S, Van Leent EJ, Ho V *et al*. Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone acetate ointment in children with atopic dermatitis. *J Allergy Clin Immunol* 2002; **109**: 539–546.
92 Luger T, Van-Leent EJ, Graeber M *et al*. SDZ ASM 981: an emerging safe and effective treatment for atopic dermatitis. *Br J Dermatol* 2001; **144**: 788–794.
93 Thaci D, Salgo R. Malignancy concerns of topical calcineurin inhibitors for atopic dermatitis: facts and controversies. *Clin Dermatol* 2010; **28**: 52–56.
94 Luger T, Boguniewicz M, Carr W *et al*. Pimecrolimus in atopic dermatitis: consensus on safety and the need to allow use in infants. *Pediatr Allergy Immunol* 2015; **26**: 306–315.
95 Sigurgeirsson B, Boznanski A, Todd G *et al*. Safety and efficacy of pimecrolimus in atopic dermatitis: a 5-year randomized trial. *Pediatrics* 2015; **135**: 597–606.
96 Reitamo S, Rustin M, Harper J *et al*. A 4-year follow-up study of atopic dermatitis therapy with 0.1% tacrolimus ointment in children and adult patients. *Br J Dermatol* 2008; **159**: 942–951.
97 Bornhövd EC, Burgdorf WHC, Wollenberg A. Immunomodulatory macrolactams for topical treatment of inflammatory skin diseases. *Curr Opin Investig Drugs* 2002; **3**: 708–712.
98 Lübbe J, Pournaras CC, Saurat JH. Eczema herpeticum during treatment of atopic dermatitis with 0.1% tacrolimus ointment. *Dermatology* 2000; **201**: 249–251.
99 Wetzel S, Wollenberg A. Eczema molluscatum in tacrolimus treated atopic dermatitis. *Eur J Dermatol* 2004; **14**: 73–74.
100 Seegraber M, Worm M, Werfel T *et al*. Recurrent eczema herpeticum - a retrospective European multicenter study evaluating the clinical characteristics of eczema herpeticum cases in atopic dermatitis patients. *J Eur Acad Dermatol Venereol* 2019; **34**: 1074–1079.
101 Queille-Roussel C, Paul C, Duteil L *et al*. The new topical ascomycin derivative SDZ ASM 981 does not induce skin atrophy when applied to normal skin for 4 weeks: a randomized, double-blind controlled study. *Br J Dermatol* 2001; **144**: 507–513.
102 Reitamo S, Rissanen J, Remitz A *et al*. Tacrolimus ointment does not affect collagen synthesis: results of a single-center randomized trial. *J Invest Dermatol* 1998; **111**: 396–398.
103 Arellano FM, Wentworth CE, Arana A, Fernandez C, Paul CF. Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. *J Invest Dermatol* 2007; **127**: 808–816.
104 Margolis DJ, Hoffstad O, Bilker W. Lack of association between exposure to topical calcineurin inhibitors and skin cancer in adults. *Dermatology* 2007; **214**: 289–295.
105 Deleuran M, Vestergaard C, Volund A, Thestrup-Pedersen K. Topical calcineurin inhibitors, topical glucocorticoids and cancer in children: a nationwide study. *Acta Derm Venereol* 2016; **96**: 834–835.
106 van den Bogaard EH, Bergboer JG, Vonk-Bergers M *et al*. Coal tar induces AHR-dependent skin barrier repair in atopic dermatitis. *J Clin Invest* 2013; **123**: 917–927.
107 Peppers J, Paller AS, Maeda-Chubachi T *et al*. A phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of atopic dermatitis. *J Am Acad Dermatol* 2019; **80**: 89–98.e3.
108 Guttman-Yassky E, Hanifin JM, Boguniewicz M *et al*. The role of phosphodiesterase 4 in the pathophysiology of atopic dermatitis and the perspective for its inhibition. *Exp Dermatol* 2019; **28**: 3–10.
109 Yang H, Wang J, Zhang X *et al*. Application of topical phosphodiesterase 4 inhibitors in mild to moderate atopic dermatitis: a systematic review and meta-analysis. *JAMA Dermatol* 2019; **155**: 585–593.
110 Paller AS, Tom WL, Lebwohl MG *et al*. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol* 2016; **75**: 494–503 e496.
111 Eichenfield LF, Call RS, Forsha DW *et al*. Long-term safety of crisaborole ointment 2% in children and adults with mild to moderate atopic dermatitis. *J Am Acad Dermatol* 2017; **77**: 641–649.e5.
112 Wollenberg A, Reitamo S, Atzori F *et al*. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. *Allergy* 2008; **63**: 742–750.
113 Thaci D, Reitamo S, Gonzalez Ensenat MA *et al*. Proactive disease management with 0.03% tacrolimus ointment for children with atopic dermatitis: results of a randomized, multicentre, comparative study. *Br J Dermatol* 2008; **159**: 1348–1356.
114 Berth-Jones J, Damstra RJ, Golsch S *et al*. Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. *Br Med J* 2003; **326**: 1367.
115 Peserico A, Stadtler G, Sebastian M, Fernandez RS, Vick K, Bieber T. Reduction of relapses of atopic dermatitis with methylprednisolone aceponate cream twice weekly in addition to maintenance treatment with emollient: a multicentre, randomized, double-blind, controlled study. *Br J Dermatol* 2008; **158**: 801–807.
116 Chittock J, Brown K, Cork MJ, Danby SG. Comparing the effect of a twice-weekly tacrolimus and betamethasone valerate dose on the subclinical epidermal barrier defect in atopic dermatitis. *Acta Derm Venereol* 2015; **95**: 653–658.
117 Sher LG, Chang J, Patel IB, Balkrishnan R, Fleischer AB Jr. Relieving the pruritus of atopic dermatitis: a meta-analysis. *Acta Derm Venereol* 2012; **92**: 455–461.
118 Wollenberg A, Sidhu MK, Odeyemi I *et al*. Economic evaluation of maintenance treatment with tacrolimus 0.1% ointment in adults with moderate to severe atopic dermatitis. *Br J Dermatol* 2008; **159**: 1322–1330.
119 Fukuie T, Hirakawa S, Narita M *et al*. Potential preventive effects of proactive therapy on sensitization in moderate to severe childhood atopic dermatitis: a randomized, investigator-blinded, controlled study. *J Dermatol* 2016; **43**: 1283–1292.
120 Garritsen FM, Brouwer MW, Limpens J, Spuls PI. Photo(chemo)therapy in the management of atopic dermatitis: an updated systematic review with implications for practice and research. *Br J Dermatol* 2014; **170**: 501–513.
121 Gambichler T, Kreuter A, Tomi NS, Othlinghaus N, Altmeyer P, Skrygan M. Gene expression of cytokines in atopic eczema before and after ultraviolet al phototherapy. *Br J Dermatol* 2008; **158**: 1117–1120.
122 Dotterud LK, Wilsgaard T, Vorland LH, Falk ES. The effect of UVB radiation on skin microbiota in patients with atopic dermatitis and healthy controls. *Int J Circumpolar Health* 2008; **67**: 254–260.
123 Hong SP, Kim MJ, Jung MY *et al*. Biopositive effects of low-dose UVB on epidermis: coordinate upregulation of antimicrobial peptides and permeability barrier reinforcement. *J Invest Dermatol* 2008; **128**: 2880–2887.

124 Margolis DJ, Abuabara K, Hoffstad OJ, Wan J, Raimondo D, Bilker WB. Association between malignancy and topical use of pimecrolimus. *JAMA Dermatol* 2015; **151**: 594–599.

125 Mavilia L, Mori M, Rossi R, Campolmi P, Puglisi Guerra A, Lotti T. 308 nm monochromatic excimer light in dermatology: personal experience and review of the literature. *Giornale Italiano di Dermatol Venereol* 2008; **143**: 329–337.

126 Becker D, Langer E, Seemann M *et al*. Clinical efficacy of blue light full body irradiation as treatment option for severe atopic dermatitis. *PLoS One* 2011; **6**: e20566.

127 Gambichler T, Othlinghaus N, Tomi NS *et al*. Medium-dose ultraviolet (UV) A1 vs. narrowband UVB phototherapy in atopic eczema: a randomized crossover study. *Br J Dermatol* 2009; **160**: 652–658.

128 Skaaby T, Husemoen LL, Thyssen JP *et al*. Filaggrin loss-of-function mutations and incident cancer: a population-based study. *Br J Dermatol* 2014; **171**: 1407–1414.

129 Kaae J, Szecsi PB, Meldgaard M *et al*. Individuals with complete filaggrin deficiency may have an increased risk of squamous cell carcinoma. *Br J Dermatol* 2014; **170**: 1380–1381.

130 Darsow U. Allergen-specific immunotherapy for atopic eczema – updated. *Curr Opin Allergy Clin Immunol* 2012; **12**: 665–669.

131 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.

132 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 e924.

133 Matterne U, Bohmer MM, Weisshaar E, Jupiter A, Carter B, Apfelbacher CJ. Oral H1 antihistamines as 'add-on' therapy to topical treatment for eczema. *Cochrane Database Syst Rev* 2019; **1**: CD012167.

134 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.

135 Schmitt J, Buske-Kirschbaum A, Tesch F *et al*. Increased attention-deficit/hyperactivity symptoms in atopic dermatitis are associated with history of antihistamine use. *Allergy* 2018; **73**: 615–626.

136 Schaper-Gerhardt K, Rossbach K, Nikolouli E, Werfel T, Gutzmer R, Mommert S. The role of the histamine H4 receptor in atopic dermatitis and psoriasis. *Br J Pharmacol* 2018; **177**: 490–502.

137 Werfel T, Layton G, Yeadon M *et al*. Efficacy and safety of the histamine H4 receptor antagonist ZPL-3893787 in patients with atopic dermatitis. *J Allergy Clin Immunol* 2019; **143**: 1830–1837 e1834.

138 Simpson EL, Bruin-Weller M, Flohr C *et al*. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. *J Am Acad Dermatol* 2017; **77**: 623–633.

139 Izadi N, Leung DYM. Clinical approach to the patient with refractory atopic dermatitis. *Ann Allergy Asthma Immunol* 2018; **120**: 23–33 e21.

140 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.

141 Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. *Nat Rev Dis Primers* 2018; **4**: 1.

142 Ring J, Alomar A, Bieber T *et al*. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. *J Eur Acad Dermatol Venereol* 2012; **26**: 1176–1193.

143 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.

144 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.

145 Gerbens LAA, Hamann SAS, Brouwer MWD, Roekevisch E, Leeflang MMG, Spuls PI. Methotrexate and azathioprine for severe atopic dermatitis: a 5-year follow-up study of a randomized controlled trial. *Br J Dermatol* 2018; **178**: 1288–1296.

146 Goujon C, Viguier M, Staumont-Salle D *et al*. Methotrexate versus cyclosporine in adults with moderate-to-severe atopic dermatitis: a phase iii randomized noninferiority trial. *J Allergy Clin Immunol Pract* 2018; **6**: 562–569.e3

147 Dvorakova V, O'Regan GM, Irvine AD. Methotrexate for severe childhood atopic dermatitis: clinical experience in a tertiary center. *Pediatr Dermatol* 2017; **34**: 528–534.

148 van der Schaft J, Politiek K, van den Reek JM *et al*. Drug survival for azathioprine and enteric-coated mycophenolate sodium in a long-term daily practice cohort of adult patients with atopic dermatitis. *Br J Dermatol* 2016; **175**: 199–202.

149 Khan N, Abbas AM, Lichtenstein GR, Loftus EV, Jr, Bazzano LA. Risk of lymphoma in patients with ulcerative colitis treated with thiopurines: a nationwide retrospective cohort study. *Gastroenterology* 2013; **145**: 1007–1015.e3.

150 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.e5.

151 Caufield M, Tom WL. Oral azathioprine for recalcitrant pediatric atopic dermatitis: clinical response and thiopurine monitoring. *J Am Acad Dermatol* 2013; **68**: 29–35.

152 Waxweiler WT, Agans R, Morrell DS. Systemic treatment of pediatric atopic dermatitis with azathioprine and mycophenolate mofetil. *Pediatr Dermatol* 2011; **28**: 689–694.

153 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.

154 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.

155 Simpson EL, Lacour JP, Spelman L *et al*. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. *Br J Dermatol* 2020; **183**: 242–255.

156 Guttman-Yassky E, Thaci D, Pangan AL *et al*. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2020; **145**: 877–884.

157 Gooderham MJ, Forman SB, Bissonnette R *et al*. Efficacy and safety of oral janus kinase 1 inhibitor abrocitinib for patients with atopic dermatitis: a phase 2 randomized clinical trial. *JAMA Dermatol* 2019; **155**: 1371.

158 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.

159 Grahovac M, Molin S, Prinz JC, Ruzicka T, Wollenberg A. Treatment of atopic eczema with oral alitretinoin. *Br J Dermatol* 2010; **162**: 217–218.

160 Murase JE, Heller MM, Butler DC. Safety of dermatologic medications in pregnancy and lactation: part I. Pregnancy. *J Am Acad Dermatol* 2014; **70**: 401.e1–401.e14.

161 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.

162 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.

163 Simpson EL, Akinlade B, Ardeleanu M. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med* 2017; **376**: 1090–1091.

164 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.

165 Barbarot S, Wollenberg A, Silverberg JI *et al*. Dupilumab provides rapid and sustained improvement in SCORAD outcomes in adults with moderate-to-severe atopic dermatitis: combined results of four randomized phase 3 trials. *J Dermatolog Treat* 2020; **1–34**.

166 de Wijs LEM, Bosma AL, Erler NS *et al*. Effectiveness of dupilumab treatment in 95 patients with atopic dermatitis: daily practice data. *Br J Dermatol* 2019; **182**: 418–426.

167 Faiz S, Giovannelli J, Podevin C *et al*. Effectiveness and safety of dupilumab for the treatment of atopic dermatitis in a real-life French multicenter adult cohort. *J Am Acad Dermatol* 2019; **81**: 143–151.

168 Abraham S, Haufe E, Harder I *et al*. Implementation of dupilumab in routine care of atopic eczema: results from the German national registry TREATgermany. *Br J Dermatol* 2020; **183**: 382–384.

169 Akinlade B, Guttman-Yassky E, de Bruin-Weller M *et al*. Conjunctivitis in dupilumab clinical trials. *Br J Dermatol* 2019; **181**: 459–473.

170 Wollenberg A, Ariens L, Thurau S, van Luijk C, Seegraber M, de Bruin-Weller M. Conjunctivitis occurring in atopic dermatitis patients treated with dupilumab-clinical characteristics and treatment. *J Allergy Clin Immunol Pract* 2018; **6**: 1778–1780.e1.

171 Thyssen JP, de Bruin-Weller MS, Paller AS *et al*. Conjunctivitis in atopic dermatitis patients with and without dupilumab therapy - international eczema council survey and opinion. *J Eur Acad Dermatol Venereol* 2019; **33**: 1224–1231.

172 Aszodi N, Thurau S, Seegraber M, de Bruin-Weller M, Wollenberg A. Management of dupilumab-associated conjunctivitis in atopic dermatitis. *J Dtsch Dermatol Ges* 2019; **17**: 488–491.

173 de Wijs LEM, Nguyen NT, Kunkeler ACM, Nijsten T, Damman J, Hijnen DJ. Clinical and histopathological characterization of paradoxical head and neck erythema in patients with atopic dermatitis treated with dupilumab: a case series. *Br J Dermatol* 2020; 183: 745–749.

174 Soria A, Du-Thanh A, Seneschal J *et al*. Development or exacerbation of head and neck dermatitis in patients treated for atopic dermatitis with dupilumab. *JAMA Dermatol* 2019; **155**: 1312–1315.

175 Wollenberg A, Beck LA, Blauvelt A *et al*. Laboratory safety of dupilumab in moderate-to-severe atopic dermatitis: results from three phase III trials (LIBERTY AD SOLO 1, LIBERTY AD SOLO 2, LIBERTY AD CHRONOS). *Br J Dermatol* 2019; **182**: 1120–1135.

176 Simpson EL, Flohr C, Eichenfield LF *et al*. Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: a randomized, placebo-controlled phase II trial (TREBLE). *J Am Acad Dermatol* 2018; **78**: 863–871.e11.

177 Wollenberg A, Howell MD, Guttman-Yassky E *et al*. Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb. *J Allergy Clin Immunol* 2019; **143**: 135–141.

178 Guttman-Yassky E, Brunner PM, Neumann AU *et al*. Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments: a randomized, double-blind, phase 2a trial. *J Am Acad Dermatol* 2018; **78**: 872–881.e6.

179 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.

180 Silverberg JI, Pinter A, Pulka G *et al*. Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus. *J Allergy Clin Immunol* 2019; **145**: 173–182.

181 Kabashima K, Furue M, Hanifin JM *et al*. Nemolizumab in patients with moderate-to-severe atopic dermatitis: randomized, phase II, long-term extension study. *J Allergy Clin Immunol* 2018; **142**: 1121–1130.e7.

182 Stander S, Yosipovitch G, Legat FJ *et al*. Trial of nemolizumab in moderate-to-severe prurigo nodularis. *N Engl J Med* 2020; **382**: 706–716.

183 Chen YL, Gutowska-Owsiak D, Hardman CS *et al*. Proof-of-concept clinical trial of etokimab shows a key role for IL-33 in atopic dermatitis pathogenesis. *Sci Transl Med* 2019; **11**: eaax2945.

184 Weidinger S, Novak N. Atopic dermatitis. *Lancet* 2016; **387**: 1109–1122.

185 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.

186 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.

187 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.

188 Iwase T, Uehara Y, Shinji H *et al*. Staphylococcus epidermidis Esp inhibits *Staphylococcus aureus* biofilm formation and nasal colonization. *Nature* 2010; **465**: 346–349.

189 Geoghegan JA, Irvine AD, Foster TJ. *Staphylococcus aureus* and atopic dermatitis: a complex and evolving relationship. *Trends Microbiol* 2018; **26**: 484–497.

190 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 e421–428.

191 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.

192 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.

193 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.

194 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.

195 Chopra R, Vakharia PP, Sacotte R, Silverberg JI. Efficacy of bleach baths in reducing severity of atopic dermatitis: a systematic review and meta-analysis. *Ann Allergy Asthma Immunol* 2017; **119**: 435–440.

196 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.

197 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.

198 Kim J, Kim BE, Ahn K, Leung DYM. Interactions between atopic dermatitis and *Staphylococcus aureus* infection: clinical implications. *Allergy Asthma Immunol Res* 2019; **11**: 593–603.

199 Harkins CP, Holden MTG, Irvine AD. Antimicrobial resistance in atopic dermatitis: Need for an urgent rethink. *Ann Allergy Asthma Immunol* 2019; **122**: 236–240.

200 Briscoe CC, Reich P, Fritz S, Coughlin CC. *Staphylococcus aureus* antibiotic susceptibility patterns in pediatric atopic dermatitis. *Pediatr Dermatol* 2019; **36**: 482–485.

201 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.

202 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.

203 Srour J, Berg E, Mahltig B, Smolik T, Wollenberg A. Evaluation of antimicrobial textiles for atopic dermatitis. *J Eur Acad Dermatol Venereol* 2019; **33**: 384–390.

204 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.

205 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.

206 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.

207 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.

208 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.

209 Thomas KS, Bradshaw LE, Sach TH *et al*. 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.

210 Hofer D. A real-life based evaluation of the effectiveness of antibacterial fabrics in treating atopic dermatitis. *Dermatol Res Pract* 2018; **2018**: 7043438.

211 Wollenberg A, Wagner M, Gunther S *et al*. Plasmacytoid dendritic cells: a new cutaneous dendritic cell subset with distinct role in inflammatory skin diseases. *J Invest Dermatol* 2002; **119**: 1096–1102.

212 Howell MD, Wollenberg A, Gallo RL *et al*. Cathelicidin deficiency predisposes to eczema herpeticum. *J Allergy Clin Immunol* 2006; **117**: 836–841.

213 Ong PY, Leung DY. Bacterial and viral infections in atopic dermatitis: a comprehensive review. *Clin Rev Allergy Immunol* 2016; **51**: 329–337.

214 Leung DY. Why is eczema herpeticum unexpectedly rare? *Antiviral Res* 2013; **98**: 153–157.

215 Traidl S, Kienlin P, Begemann G *et al*. Patients with atopic dermatitis and history of eczema herpeticum elicit herpes simplex virus-specific type 2 immune responses. *J Allergy Clin Immunol* 2018; **141**: 1144–1147.e5.

216 Wollenberg A. Eczema herpeticum. *Chem Immunol Allergy* 2012; **96**: 89–95.

217 Beck KM, Seitzman GD, Yang EJ, Sanchez IM, Liao W. Ocular co-morbidities of atopic dermatitis. part i: associated ocular diseases. *Am J Clin Dermatol* 2019; **20**: 797–805.

218 Eichenfield LF, Bieber T, Beck LA *et al*. Infections in dupilumab clinical trials in atopic dermatitis: a comprehensive pooled analysis. *Am J Clin Dermatol* 2019; **20**: 443–456.

219 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.

220 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.

221 Silverberg NB. Molluscum contagiosum virus infection can trigger atopic dermatitis disease onset or flare. *Cutis* 2018; **102**: 191–194.

222 Osier E, Eichenfield LF. The utility of cantharidin for the treatment of molluscum contagiosum. *Pediatr Dermatol* 2015; **32**: 295.

223 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.

224 Wollenberg A, Engler R. Smallpox, vaccination and adverse reactions to smallpox vaccine. *Curr Opin Allergy Clin Immunol* 2004; **4**: 271–275.

225 Reed JL, Scott DE, Bray M. Eczema vaccinatum. *Clin Infect Dis* 2012; **54**: 832–840.

226 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.

227 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.

228 Lynch MD, Sears A, Cookson H *et al*. Disseminated coxsackievirus A6 affecting children with atopic dermatitis. *Clin Exp Dermatol* 2015; **40**: 525–528.

229 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.

230 Glatz M, Bosshard PP, Hoetzenecker W, Schmid-Grendelmeier P. The role of Malassezia spp. in atopic dermatitis. *J Clin Med* 2015; **4**: 1217–1228.

231 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.

232 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.

233 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.

234 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.

235 Simpson EL, Basco M, Hanifin J. A cross-sectional survey of complementary and alternative medicine use in patients with atopic dermatitis. *Am J Contact Dermatol* 2003; **14**: 144–147.

236 Kim JE, Lee YB, Lee JH *et al*. Disease awareness and management behavior of patients with atopic dermatitis: a questionnaire survey of 313 patients. *Ann Dermatol* 2015; **27**: 40–47.

237 Lu CL, Liu XH, Stub T *et al*. Complementary and alternative medicine for treatment of atopic eczema in children under 14 years old: a systematic review and meta-analysis of randomized controlled trials. *BMC Complement Altern Med* 2018; **18**: 260.

238 Shi K, Lio PA. Alternative treatments for atopic dermatitis: an update. *Am J Clin Dermatol* 2019; **20**: 251–266.

239 Gu S, Yang AW, Xue CC *et al*. Chinese herbal medicine for atopic eczema. *Cochrane Database Syst Rev* 2013; **4**: CD008642.

240 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.

241 Gunaratne AW, Makrides M, Collins CT. Maternal prenatal and/or postnatal n-3 long chain polyunsaturated fatty acids (LCPUFA) supplementation for preventing allergies in early childhood. *Cochrane Database Syst Rev* 2015; **7**: CD010085.

242 Kim DY, Park HS, Cho S, Yoon HS. The quality of reporting randomized controlled trials in the dermatology literature in an era where the CONSORT statement is a standard. *Br J Dermatol* 2019; **180**: 1361–1367.

243 Ornelas J, Routt E, Kallis P, Lev-Tov H. Use of the hCONSORT criteria as a reporting standard for herbal interventions for common dermatoses: a systematic review. . *Br J Dermatol* 2018; **178**: 889–896.

244 Schmitt J, Williams H.Group HD. Harmonising Outcome Measures for Eczema (HOME). Report from the First International Consensus Meeting (HOME 1), 24 July 2010 Munich, Germany. *Br J Dermatol* 2010; **163**: 1166–1168.

245 Chalmers JR, Thomas KS, Apfelbacher C *et al*. Report from the fifth international consensus meeting to harmonize core outcome measures for atopic eczema/dermatitis clinical trials (HOME initiative). *Br J Dermatol* 2018; **178**: e332–e341.

246 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.

247 Benson AA, Toh JA, Vernon N, Jariwala SP. The role of vitamin D in the immunopathogenesis of allergic skin diseases. *Allergy* 2012; **67**: 296–301.

248 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.

249 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.

250 Huang CM, Lara-Corrales I, Pope E. Effects of vitamin D levels and supplementation on atopic dermatitis: a systematic review. *Pediatr Dermatol* 2018; **35**: 754–760.

251 Yepes-Nunez JJ, Brozek JL, Fiocchi A *et al*. Vitamin D supplementation in primary allergy prevention: systematic review of randomized and non-randomized studies. *Allergy* 2018; **73**: 37–49.

252 Isolauri E, Sütas Y, Kankaanpää P, Arvilommi H, Salminen S. Probiotics: effects on immunity. *Am J Clin Nutr* 2001; **73**: 444–450.

253 Rather IA, Bajpai VK, Kumar S, Lim J, Paek WK, Park YH. Probiotics and atopic dermatitis: an overview. *Front Microbiol* 2016; **7**: 507.

254 Huang R, Ning H, Shen M, Li J, Zhang J, Chen X. Probiotics for the treatment of atopic dermatitis in children: a systematic review and meta-analysis of randomized controlled trials. *Front Cell Infect Microbiol* 2017; **7**: 392.

255 Doege K, Grajecki D, Zyriax BC, Detinkina E, Zu Eulenburg C, Buhling KJ. Impact of maternal supplementation with probiotics during pregnancy on atopic eczema in childhood–a meta-analysis. *Br J Nutr* 2012; **107**: 1–6.

256 Pelucchi C, Chatenoud L, Turati F *et al*. Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis. *Epidemiology* 2012; **23**: 402–414.

257 Makrgeorgou A, Leonardi-Bee J, Bath-Hextall FJ *et al*. Probiotics for treating eczema. *Cochrane Database Syst Rev* 2018; **11**: CD006135.

258 Schimke LF, Sawalle-Belohradsky J, Roesler J *et al*. Diagnostic approach to the hyper-IgE syndromes: immunologic and clinical key findings to differentiate hyper-IgE syndromes from atopic dermatitis. *J Allergy Clin Immunol* 2010; **126**: 611–617.e1.

259 Su JC, Dailey R, Zallmann M *et al*. Determining Effects of Superfine Sheep wool in INfantile Eczema (DESSINE): a randomized paediatric crossover study. *BrJ Dermatol* 2017; **177**: 125–133.

260 Langan SM, Silcocks P, Williams HC. What causes flares of eczema in children? *Br J Dermatol* 2009; **161**: 640–646.

261 Wood RA, Sicherer SH, Vickery BP *et al*. The natural history of milk allergy in an observational cohort. *J Allergy Clin Immunol* 2013; **131**: 805–812.

262 Chen MH, Su TP, Chen YS *et al*. Is atopy in early childhood a risk factor for ADHD and ASD? A longitudinal study. *J Psychosom Res* 2014; **77**: 316–321.

263 Simonsen AB, Johansen JD, Deleuran M, Mortz CG, Skov L, Sommerlund M. Children with atopic dermatitis may have unacknowledged contact allergies contributing to their skin symptoms. *J Eur Acad Dermatol Venereol* 2018; **32**: 428–436.

264 Lukas A, Wolf G, Folster-Holst R. Special features of topical and systemic dermatologic therapy in children. *J Dtsch Dermatol Ges* 2006; **4**: 658–677; quiz 679–680.

265 Proudfoot LE, Powell AM, Ayis S *et al*. The European TREatment of severe Atopic eczema in children Taskforce (TREAT) survey. *Br J Dermatol* 2013; **169**: 901–909.

266 Deo M, Yung A, Hill S, Rademaker M. Methotrexate for treatment of atopic dermatitis in children and adolescents. *Int J Dermatol* 2014; **53**: 1037–1041.

267 Anderson K, Putterman E, Rogers RS, Patel D, Treat JR, Castelo-Soccio L. Treatment of severe pediatric atopic dermatitis with methotrexate: a retrospective review. *Pediatr Dermatol* 2019; **36**: 298–302.

268 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.

269 Knopfel N, Noguera-Morel L, Hernandez-Martin A, Torrelo A. Methotrexate for severe nummular eczema in children: efficacy and tolerability in a retrospective study of 28 patients. *Pediatr Dermatol* 2018; **35**: 611–615.

270 Boozalis E, Grossberg AL, Puttgen KB, Cohen BA, Kwatra SG. Itching at night: a review on reducing nocturnal pruritus in children. *Pediatr Dermatol* 2018; **35**: 560–565.

271 James JM, Burks AW, Roberson PK, Sampson HA. Safe administration of the measles vaccine to children allergic to eggs. *N Engl J Med* 1995; **332**: 1262–1266.

272 Mason JM, Carr J, Buckley C *et al*. Improved emollient use reduces atopic eczema symptoms and is cost neutral in infants: before-and-after evaluation of a multifaceted educational support programme. *BMC Dermatol* 2013; **13**: 7.

273 Gabeff R, Assathiany R, Barbarot S, Salinier C, Stalder JF. Dermatite atopique: evaluation de la perception d'un plan d'action personnalise aupres de pediatres liberaux. *Arch Pediatr* 2014; **21**: 705–708.

274 Frisen A. Measuring health-related quality of life in adolescence. *Acta Paediatr* 2007; **96**: 963–968.

275 Oranje AP, Devillers AC, Kunz B *et al*. Treatment of patients with atopic dermatitis using wet-wrap dressings with diluted steroids and/or emollients. An expert panel's opinion and review of the literature. *J Eur Acad Dermatol Venereol* 2006; **20**: 1277–1286.

276 Kosse RC, Bouvy ML, Daanen M, de Vries TW, Koster ES. Adolescents' perspectives on atopic dermatitis treatment-experiences, preferences, and beliefs. *JAMA Dermatol* 2018; **154**: 824–827.

277 Silverberg NB, Duran-McKinster C. Special considerations for therapy of pediatric atopic dermatitis. *Dermatol Clin* 2017; **35**: 351–363.

278 Tuchman M, Silverberg JI, Jacob SE, Silverberg N. Nickel contact dermatitis in children. *Clin Dermatol* 2015; **33**: 320–326.

279 Xie QW, Dai X, Tang X, Chan CHY, Chan CLW. Risk of mental disorders in children and adolescents with atopic dermatitis: a systematic review and meta-analysis. *Front Psychol* 2019; **10**: 1773.

280 Halvorsen JA, Lien L, Dalgard F, Bjertness E, Stern RS. Suicidal ideation, mental health problems, and social function in adolescents with eczema: a population-based study. *J Invest Dermatol* 2014; **134**: 1847–1854.

281 Cheng CM, Hsu JW, Huang KL *et al*. Risk of developing major depressive disorder and anxiety disorders among adolescents and adults with atopic dermatitis: a nationwide longitudinal study. *J Affect Disord* 2015; **178**: 60–65.

282 Becker-Haimes EM, Diaz KI, Haimes BA, Ehrenreich-May J. Anxiety and atopic disease: comorbidity in a youth mental health setting. *Child Psychiatry Hum Dev* 2017; **48**: 528–536.

283 Magin P. Appearance-related bullying and skin disorders. *Clin Dermatol* 2013; **31**: 66–71.

284 Brenninkmeijer EE, Legierse CM, Sillevis Smitt JH, Last BF, Grootenhuis MA, Bos JD. The course of life of patients with childhood atopic dermatitis. *Pediatr Dermatol* 2009; **26**: 14–22.

285 Hon KL, Pong NH, Poon TC *et al*. Quality of life and psychosocial issues are important outcome measures in eczema treatment. *J Dermatolog Treat* 2015; **26**: 83–89.

286 Nguyen CM, Koo J, Cordoro KM. Psychodermatologic effects of atopic dermatitis and acne: a review on self-esteem and identity. *Pediatr Dermatol* 2016; **33**: 129–135.

287 Eckert L, Gupta S, Amand C, Gadkari A, Mahajan P, Gelfand JM. Impact of atopic dermatitis on health-related quality of life and productivity in adults in the United States: an analysis using the national health and wellness survey. *J Am Acad Dermatol* 2017; **77**: 274–279.e3.

288 Brew BK, Soderberg J, Lundholm C, Afshar S, Holmberg K, Almqvist C. Academic achievement of adolescents with asthma or atopic disease. *Clin Exp Allergy* 2019; **49**: 892–899.

289 Bandier J, Carlsen BC, Rasmussen MA, Petersen LJ, Johansen JD. Skin reaction and regeneration after single sodium lauryl sulfate exposure stratified by filaggrin genotype and atopic dermatitis phenotype. *Br J Dermatol* 2015; **172**: 1519–1529.
290 Ruff SMD, Engebretsen KA, Zachariae C *et al.* The association between atopic dermatitis and hand eczema: a systematic review and meta-analysis. *Br J Dermatol* 2018; **178**: 879–888.
291 Evers AW, Schut C, Gieler U, Spillekom-van Koulil S, van Beugen S. Itch management: psychotherapeutic approach. *Curr Probl Dermatol* 2016; **50**: 64–70.
292 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.
293 Mitchell AE, Fraser JA, Morawska A, Ramsbotham J, Yates P. Parenting and childhood atopic dermatitis: a cross-sectional study of relationships between parenting behaviour, skin care management, and disease severity in young children. *Int J Nurs Stud* 2016; **64**: 72–85.
294 Rosenbaum MS, Ayllon T. The behavioral treatment of neurodermatitis through habit-reversal. *Behav Res Ther* 1981; **19**: 313–318.
295 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.
296 Chida Y, Steptoe A, Hirakawa N, Sudo N, Kubo C. The effects of psychological intervention on atopic dermatitis. A systematic review and meta-analysis. *Int Arch Allergy Immunol* 2007; **144**: 1–9.
297 Gieler U, Kupfer J, Niemeier V, Brosig B, Standier U. Atopic eczema prevention programs – a new therapeutic concept for secondary prevention. *Dermatol Psychosom* 2000; **1**: 138–147.
298 Grossman SK, Schut C, Kupfer J, Valdes-Rodriguez R, Gieler U, Yosipovitch G. Experiences with the first eczema school in the United States. *Clin Dermatol* 2018; **36**: 662–667.
299 Lee Y, Oh J. Educational programs for the management of childhood atopic dermatitis: an integrative review. *Asian Nurs Res (Korean Soc Nurs Sci)* 2015; **9**: 185–193.
300 Lange S, Zschocke I, Langhardt S, Amon U, Augustin M. Effects of combined dermatological and behavioural medicine therapy in hospitalized patients with psoriasis and atopic dermatitis. *Hautarzt* 1999; **50**: 791–797.
301 Liang Y, Tian J, Shen CP *et al.* Therapeutic patient education in children with moderate to severe atopic dermatitis: a multicenter randomized controlled trial in China. *Pediatr Dermatol* 2018; **35**: 70–75.
302 Morawska A, Mitchell AE, Burgess S, Fraser J. Effects of Triple P parenting intervention on child health outcomes for childhood asthma and eczema: randomised controlled trial. *Behav Res Ther* 2016; **83**: 35–44.
303 Staab D, von Rueden U, Kehrt R *et al.* Evaluation of a parental training program for the management of childhood atopic dermatitis. *Pediatr Allergy Immunol* 2002; **13**: 84–90.
304 Stangier U, Ehlers A, Gieler U. Predicting long-term outcome in group treatment of atopic dermatitis. *Psychother Psychosom* 2004; **73**: 293–301.
305 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.
306 Yoo JB, De Gagne JC, Jeong SS, Jeong CW. Effects of a hybrid education programme for Korean mothers of children with atopic dermatitis. *Acta Derm Venereol* 2018; **98**: 329–334.
307 Pickett K, Loveman E, Kalita N, Frampton GK, Jones J. Educational interventions to improve quality of life in people with chronic inflammatory skin diseases: systematic reviews of clinical effectiveness and cost-effectiveness. *Health Technol Assess* 2015; **19**: 1–176, v–vi.
308 Spielman SC, LeBovidge JS, Timmons KG, Schneider LC. A review of multidisciplinary interventions in atopic dermatitis. *J Clin Med* 2015; **4**: 1156–1170.
309 Ersser SJ, Cowdell F, Latter S *et al.* Psychological and educational interventions for atopic eczema in children. *Cochrane Database Syst Rev* 2014; **1**: CD004054.
310 Haubrock M, Daschner A, Diepgen T *et al.* Gesundheitsökonomische Aspekte der Prävention im Rahmen des Modellvorhabens zur besseren Vorsorge und Versorgung von Kindern und Jugendlichen mit atopischem Ekzem (Neurodermitis) – Ein nationales, prospektives Multizenterprojekt zur Entwicklung und Erprobung eines standardisierten Patientenschulungsprogramms (GADIS). *Gesund Ökon Qual Manag* 2009; **14**: 191–199.
311 Bathe A, Matterne U, Dewald M, Grande T, Weisshaar E. Educational multidisciplinary training programme for patients with chronic pruritus. *Acta Derm Venereol* 2009; **89**: 498–501.
312 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.
313 Hoegl L, Fichter M, Plewig G. Inpatient behavioral medicine in chronic skin diseases. *Hautarzt* 1998; **49**: 270–275.
314 Daunton A, Bridgett C, Goulding JM. Habit reversal for refractory atopic dermatitis: a review. *Br J Dermatol* 2016; **174**: 657–659.
315 Gupta MA. Evaluation and treatment of "psychogenic" pruritus and self-excoriation. *J Am Acad Dermatol* 1995; **32**: 532–533.
316 Schut C, Weik U, Tews N, Gieler U, Deinzer R, Kupfer J. Psychophysiological effects of stress management in patients with atopic dermatitis: a randomized controlled trial. *Acta Derm Venereol* 2013; **93**: 57–61.
317 Wittkowski A, Richards HL. How beneficial is cognitive behaviour therapy in the treatment of atopic dermatitis? A single-case study. *Psychol Health Med* 2007; **12**: 445–449.
318 Craddock MF, Blondin HM, Youssef MJ *et al.* Online education improves pediatric residents' understanding of atopic dermatitis. *Pediatr Dermatol* 2018; **35**: 64–69.
319 van Beugen S, Ferwerda M, Hoeve D *et al.* Internet-based cognitive behavioral therapy for patients with chronic somatic conditions: a meta-analytic review. *J Med Internet Res* 2014; **16**: e88.
320 Bundy DG, Morawski LF, Lazorick S, Bradbury S, Kamachi K, Suresh GK. Education in quality improvement for pediatric practice: an online program to teach clinicians QI. *Acad Pediatr* 2014; **14**: 517–525.
321 Vestergaard C, Thyssen JP, Barbarot S, Paul C, Ring J, Wollenberg A. Quality of care in atopic dermatitis - a position statement by the European Task Force on Atopic Dermatitis (ETFAD). *J Eur Acad Dermatol Venereol* 2020; **34**: e136–e138.
322 Wollenberg A, Flohr C, Simon D *et al.* European Task Force on Atopic Dermatitis (ETFAD) statement on severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2)-infection and atopic dermatitis. *J Eur Acad Dermatol Venereol* 2020; **34**: e241–e242.

Appendix 1

S. Barbarot, Nantes, France; T. Bieber, Bonn, Germany; P. Chernychov, Kiev, Ukraine; S. Christen-Zäch, Lausanne, Switzerland; M.J. Cork, Sheffield, United Kingdom; U. Darsow, Munich, Germany; M. Deleuran, Aarhus, Denmark; M. de Bruin-Weller, Utrecht, The Netherlands; L. De Raeve, Brussels, Belgium; C. Flohr, London, United Kingdom; R. Fölster-Holst, Kiel, Germany; C. Gelmetti, Milan, Italy; U. Gieler, Gießen, Germany; A. Heratizadeh, Hannover, Germany; D.J. Hijnen, Rotterdam, The Netherlands; B. Kunz, Hamburg, Germany; C. Paul, Toulouse, France; J. Ring, Munich, Germany; J. Seneschal, Bordeaux, France; D. Simon, Bern, Switzerland; P. Spuls, Amsterdam, The Netherlands; J.F. Stalder, Nantes, France; A. Svensson, Malmö, Sweden; Z. Szalai, Budapest, Hungary; A. Taïeb, Bordeaux, France; J.P. Thyssen, Copenhagen, Denmark; A. Torrelo, Madrid, Spain; M. Trzeciak, Gdansk, Poland; C. Vestergaard, Aarhus, Denmark; L. von Kobyletzki, Malmö, Sweden; S. Weidinger, Kiel, Germany; T. Werfel, Hannover, Germany; A. Wollenberg, Munich, Germany