GUIDELINE

European guideline (EuroGuiDerm) on atopic eczema – part II: non-systemic treatments and treatment recommendations for special AE patient populations

A. Wollenberg,^{1,2,*} (D) M. Kinberger,³ B. Arents,⁴ N. Aszodi,¹ G. Avila Valle,³ S. Barbarot,⁵ (D) T. Bieber,⁶ H.A. Brough,⁷ P. Calzavara Pinton,⁸ S. Christen-Zäch,⁹ (D) M. Deleuran,¹⁰ M. Dittmann,³ C. Dressler,³ (D) A.H. Fink-Wagner,¹¹ N. Fosse,¹² K. Gáspár,¹³ L. Gerbens,¹⁴ U. Gieler,¹⁵ G. Girolomoni,¹⁶ (D) S. Gregoriou,¹⁷ (D) C.G. Mortz,¹⁸ A. Nast,³ (D) U. Nygaard,¹⁹ M. Redding,²⁰ E.M. Rehbinder,²¹ J. Ring,²² M. Rossi,²³ E. Serra-Baldrich,²⁴ D. Simon,²⁵ Z.Z. Szalai,²⁶ J.C. Szepietowski,²⁷ A. Torrelo,²⁸ T. Werfel,²⁹ C. Flohr^{30,31,*} (D)

¹Department of Dermatology and Allergy, LMU Munich, Munich, Germany

²Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Department of Dermatology, Brussels, Belgium

⁷Children's Allergy Service, Evelina London Children's Hospital, Guy's and St. Thomas' NHS Foundation Trust, London, and Paediatric

Allergy Group, Department of Women and Children's Health, School of Life Course Sciences, King's College London, London, UK

⁸Dermatology Department, University of Brescia, Brescia, Italy

⁹University Hospital Lausanne, Lausanne, Switzerland

¹⁰Aarhus University Hospital, Aarhus, Denmark

- ¹¹Global Allergy and Airways diseases Patient Platform GAAPP, Vienna, Austria
- ¹²Department of Dermatology, University Hospital Basel, Basel, Switzerland
- ¹³Department of Dermatology of the University of Debrecen, Debrecen, Hungary
- ¹⁴Department of Dermatology, Amsterdam UMC (University Medical Centers), Amsterdam, The Netherlands

¹⁵Department Dermatology, University of Giessen, Giessen, Germany

- ¹⁶Dermatology and Venereology Section, Department of Medicine, University of Verona, Verona, Italy
- ¹⁷Faculty of Medicine, National and Kapodistrian University of Athens, Athens, Greece
- ¹⁸Department of Dermatology and Allergy Centre, Odense University Hospital, University of Southern Denmark, Odense, Denmark
- ¹⁹Department of Dermato-Venerology, Aarhus University Hospital, Aarhus, Denmark
- ²⁰Eczema Outreach Support (UK), Linlithgow, UK
- ²¹Dermatology Department, Oslo University Hospital, Oslo, Norway
- ²²Department Dermatology Allergology Biederstein, Technical University Munich, Munich, Germany
- ²³Dermatology Unit, Spedali Civili Hospital Brescia, Brescia, Italy
- ²⁴Dermatology, Hospital of Sant Pau, Barcelona, Spain
- ²⁵Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
- ²⁶Pediatric Dermatology Unit, Heim Pál National Children's Institute Budapest, Budapest, Hungary
- ²⁷Department of Dermatology, Venereology and Allergology, Wrocław Medical University, Wrocław, Poland
- ²⁸Hospital Infantil Niño Jesús, Madrid, Spain
- ²⁹Hannover Medical School, Hanover, Germany
- ³⁰St John's Institute of Dermatology, King's College London, London, UK
- ³¹Guy's & St Thomas' NHS Foundation Trust, London, UK

*Correspondence: A. Wollenberg. E-mail: wollenberg@lrz.uni-muenchen.de and C. Flohr. E-mail: carsten.flohr@kcl.ac.uk

Abstract

24.10.2022

downloaded:

source: https://doi.org/10.48350/172663 |

The evidence- and consensus-based guideline on atopic eczema was developed in accordance with the EuroGuiDerm Guideline and Consensus Statement Development Manual. Four consensus conferences were held between December 2020 and July 2021. Twenty-nine experts (including clinicians and patient representatives) from 12 European countries participated. This second part of the guideline includes recommendations and detailed information on basic therapy with emollients and moisturizers, topical anti-inflammatory treatment, antimicrobial and antipruritic treatment and UV photo-therapy. Furthermore, this part of the guideline covers techniques for avoiding provocation factors, as well as dietary

IEADV

³Department of Dermatology, Venereology and Allergology, Division of Evidence-Based Medicine (dEBM), Charité –

Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

⁴European Federation of Allergy and Airways Diseases Patients' Associations (EFA), Brussels, Belgium

⁵Department of Dermatology, CHU Nantes, UMR 1280 PhAN, INRAE, Nantes Université, Nantes, France

⁶Department of Dermatology and Allergy, University Hospital of Bonn, Bonn, Germany

interventions, immunotherapy, complementary medicine and educational interventions for patients with atopic eczema and deals with occupational and psychodermatological aspects of the disease. It also contains guidance on treatment for paediatric and adolescent patients and pregnant or breastfeeding women, as well as considerations for patients who want to have a child. A chapter on the patient perspective is also provided. The first part of the guideline, published separately, contains recommendations and guidance on systemic treatment with conventional immunosuppressive drugs, biologics and janus kinase (JAK) inhibitors, as well as information on the scope and purpose of the guideline, and a section on guideline methodology.

Received: 17 February 2022; Accepted: 3 June 2022

Conflicts of interest

This is a short version of the EuroGuiDerm Guideline on Atopic Eczema. For introductory chapters, methods section and systemic treatment, see part 1 (https://doi.org/10.1111/jdv.18345) or for the long version, methods report (including COI disclosures) and evidence report, see https://www.edf.one/home/Guidelines/Guidelines.html.

Funding sources

The development of this EuroGuiDerm guideline was funded through the EuroGuiDerm Centre for Guideline Development. The European Dermatology Forum is responsible for fundraising and holds all of the funds it raises in one account. The EuroGuiDerm Team is not involved in fundraising or in decisions about which guidelines (GL) or consensus statements (CS) are funded. These decisions are made by the EuroGuiDerm Board of Directors independently. The EDF and any other body supporting EuroGuiDerm are never involved in developing guidelines and have no say in the content or focus of guidelines.

Overview of recommendations

General recommendations for systemic drugs in special atopic eczema patient populations (Table 1) and for

topical drugs for treatment of atopic eczema (Table 2) are given below.

	Conventional s	stemic treatments		Biologics		JAK-inhibitors		Rescue therapy
	Ciclosporin	Methotrexate	Azathioprine	Dupilumab	Tralokinumab	Baricitinib	Upadacitinib	Systemic corticosteroids
Children and adolescents with who are candidat systemic treatment	tt tes for	t	t	tt			tt	
Dose for children	licensed for ≥ 16 years commonly used dosage children: 2.5-5 mg/kg per day in two single doses	commonly used dosage children: 0.3–0.4 mg/kg per week	off label; commonly used dosage children: 1-3 mg/ kg per day	licensed for ≥ 6 years; age 6-11: from 15kg <60kg, initially 300 mg s.c. day 1 &15 followed by 300 mg Q4W, when ≥60 kg, initially 600 mg s.c. day 1 followed by 300 mg Q2W age 12-17: <60 kg: initially 400 mg s.c. day 1 followed by 200 mg Q2W, when ≥60 kg: initially 600 mg s.c. day 1 followed by 300 mg Q2W	off-label	off-label	licensed for ≥ 12 years; age 12-17 (≥ 30 kg bw): 15 mg per day	general unspecific licence for children fo steroid responsive sk disease dosage maximum: 1 mg/kg per day
Pregnancy (in candidates for system treatment)	stemic		t	0		11		t prednisolone (0.5mg/ kg/d) <i>only</i> as rescue therapy for acute flares
Breastfeeding	ł	i	i	0		ł	i	t prednisolone (0.5mg/ kg/d) only as rescue therapy for acute flares
SmPC; Q2W - once	every 2 weeks							
Symbols I	Implications (adapted from (GRADE 188)						
TT .	We believe that all or almost a	Il informed people woul	d make this choice.					
t N	We believe that most informed people would make this choice, but a substanti			ntial number would not.				
	We cannot make a recommendation.							
			•	rvention, but a substantial number would	not.			
11 1	We believe that all or almost all informed people would make a choice again		st this intervention.					

Table 1 General recommendations for systemic drugs in special AE patient populations (for details see corresponding chapter)

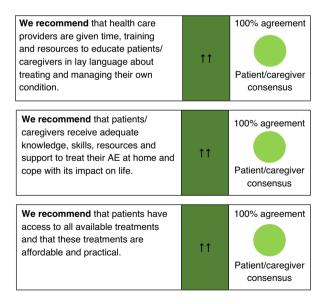
© 2022 The Authors. Journal of the European Academy of Dermatology and Venereology published by John Wiley & Sons Ltd on behalf of European Academy of Dermatology and Venereology.

Overall recommenda	tion	т	CS tt	тс	TCI 11		
		TCS class I and II	TCS class III and IV	Tacrolimus 0.1% Tacrolimus 0.03%	Pimecrolimus 1%		
For further information background text	on see	class I not suitable for long-term proactive treatment; long-term proactive treatment only class II	acute flare; proactive treatment with TCS class III class IV not for long term daily treatment or head and neck; class IV not recommended for proactive treatment either	acute flare; long-term proactive treatment; especially in face, intertriginous sites, anogenital area	acute flare; especially in face, intertriginous sites, anogenital area		
Most important side (effects	skin atrophy telangiectasia striae distensae ecchymosis hypertrichosis perioral dermatitis	skin atrophy telangiectasia striae distensae ecchymosis hypertrichosis perioral dermatitis corticosteroid addiction syndrome suppression of adrenal function	initial warmth, tingling or burning	initial warmth, tingling or burning		
		TCI class II and III are off label for pro-	active treatment	in label for proactive treatment	not suitable for proactive treatment		
Special consideration	ns				·		
Suitable for children > years of age	> 2 to < 16	yes	yes	yes (0.03%) ²	yes ²		
Suitable for babies < 2 years of age		yes	under specialist supervision	yes (0.03%)1	yes ² (from the age of three months)		
Suitable during pregna	ancy	yes	yes	yes (0.03% & 0.1%)1	yes1		
Suitable during breast	tfeeding	yes	yes	yes (0.03% & 0.1%)1	yes ¹		
Suitable for pruritus		yes	yes	yes (0.03% & 0.1%)	yes		
1 off label use 2 licensed	luse						
Symbols Implic	ations (adap	ted from GRADE 188)					
tt We be	elieve that all o	or almost all informed people would make this	choice.				
	We believe that most informed people would make this choice, but a substantial number would not.						
0 We ca	We cannot make a recommendation.						
↓ We be	elieve that mo	st informed people would make a choice agair	nst this intervention, but a substantial number wou	ld not.			
H We be	elieve that all o	or almost all informed people would make a ch	noice against this intervention.				
No rec	commendation	1.					

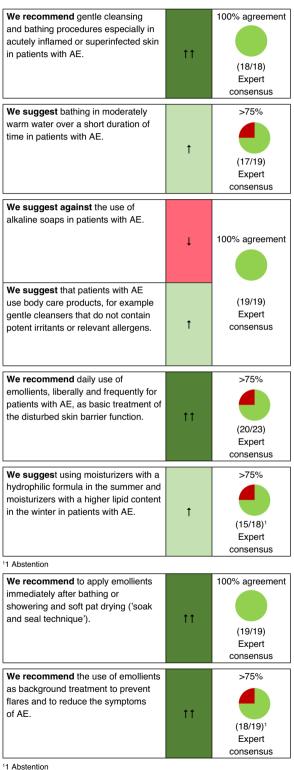
Table 2 General recommendations for topical drugs for treatment of atopic eczema (for details see corresponding chapter)

Patients' perspective

We recommend that health care providers treat each patient as a whole person, not just the skin, while considering the burden of skin disease on life.	↑ ↑	100% agreement Patient/caregiver consensus
We recommend that health care providers use the principle of shared decision-making, i.e. discuss the patients' beliefs, lifestyle and preferences when deciding on a treatment plan.	↑ ↑	100% agreement Patient/caregiver consensus
We recommend that patients with co-morbidities are treated by multi- disciplinary teams.	ţţ	100% agreement Patient/caregiver consensus



Basic emollients and moisturizers



Emollient therapy

Basic emollient therapy

Basic emollient therapy is the essence of every treatment of AE.^{1, 2} Emollients usually contain a humectant or moisturizer (promoting stratum corneum hydration) such as urea or glycerol and an occludent (reducing evaporation such as lipids or petrolatum). Recently, marketing of non-medicated 'emollients' containing active ingredients has blurred the line between pure emollients working through their physical properties and topical drugs.

Throughout this guideline, 'emollients' are defined as 'topical formulations with vehicle-type substances without active ingredients', whereas 'emollients plus' refers to 'topical formulations with vehicletype substances plus additional active, non-medicated substances³.

A Cochrane review compared emollients containing moisturizers versus no moisturizer and found that the former were better at reducing investigator-reported severity and led to fewer flares and a reduction in the use of corticosteroids.⁴ There have also been studies that have examined the use of glycerol-containing moisturizers versus vehicle or placebo.^{1,5} More participants in the glycerol group noticed skin improvement but the MID (minimal important difference) was not met.⁶

Some studies have investigated oil-containing emollients versus no treatment or vehicle and found no significant differences between the groups. In one study, there were fewer flares in the oil group and reduced use of topical corticosteroids. Overall, topical active treatment combined with emollients was more effective than emollient treatment alone with various outcomes measured.^{4,7}

It is recommended to apply emollients immediately after bathing or showering and soft pat drying. A small study suggests that an emollient applied alone without bathing may have a longer duration as measured by capacitance.⁸ Only emollient preparations free of protein allergens or haptens known to cause contact allergy (such as lanolin/wool wax alcohol or preservatives such as methylisothiazolinone)⁹ should be used, especially in children under the age of 2. The long-term use of maintenance (e.g. twice weekly) emollient therapy after remission may prolong the duration of flare-free intervals.^{7,10,11}

The direct, sole use of emollients on inflamed skin is often poorly tolerated, and it is better to treat the acute flare first with anti-inflammatory procedures including wet wraps (see chapter anti-inflammatory treatment). Emollients are the mainstay of management. Hydration of the skin is usually maintained by at least twice daily application of emollients with a hydrophilic base containing for instance 5% urea or glycerol.¹²

Galenic aspects of the formula should be considered with regard to seasonal differences (more hydrophilic in summer, more lipid content preferably in winter). Also, regional aspects of body sites involved play a role (pastes for intertriginous areas, not too greasy for the face).

Depending on the acuity of the skin condition, lipophilic bases may also be helpful, especially in more chronic conditions.

The use of barrier ointments, bath oils, shower gels, emulsions or micellar solutions that enhance the barrier effect is also recommended.

The amount of the topical that is applied is crucial; about 250 g/week are recommended.^{3,13} It may follow the fingertip unit rule: a fingertip unit (FTU) is the amount of ointment expressed from a tube with a 5 mm diameter nozzle and measured from the distal skin crease to the tip of the index finger (*ca.* 0.5 g); this is an adequate amount for application to two adult palm areas, which is approximately 2% of an adult body surface area.¹⁴

The cost of quality emollient (low in contact allergens or hazardous substances) therapies often restricts their use because such therapies are considered to be non-prescription drugs (except for paediatric patients in some European countries).¹⁵

The use of pure oil products such as coconut or olive oil instead of emulsions will dry out the skin and increase transepidermal water loss and thus is not recommended.

Emollients with non-medicated, active ingredients (emollients plus)

Several non-medicated products for topical treatment of AE contain putative active ingredients but neither fulfill the definition of, nor need a licence as, a topical drug. These products, referred to as 'emollients plus' by the European guideline since 2018, may contain, for example, flavonoids such as licochalcone A, saponins and riboflavins from protein-free oat plantlet extracts,¹⁰ bacterial lysates from Aquaphilus dolomiae or Vitreoscilla filiformis species,^{16–18} or a synthetic derivative of menthol such as menthoxypropanediol.³

Oral supplementation with unsaturated fatty acids, such as gammalinolenic acid from evening primrose oil or eicosapentaenoic acid from fish oils, has been studied as a way to improve barrier function and enhance patient acceptance, but has shown conflicting results.¹⁹ The efficacy of topical evening primerose oil-containing emollients depends on the choice of vehicle.²⁰

To improve the moisturizing effect of the emollient, several ingredients are used such as urea or glycerol or propylene glycol. Emollients can also be enriched by other ingredients such as moisturizers or tannin, ammonium bituminosulfonate, flavo-noids or unsaturated fatty acids such as omega-3 or omega-6 compounds.

Prevention aspect

Emollients have a definite place in secondary and tertiary prevention in patients with AE. There is controversial evidence on primary preventive effects of emollients: newborns with high risk of atopy/AE who were treated daily with emollients developed less atopic dermatitis or allergic sensitisations in the first year of life.^{21, 22} Two larger and longer randomized controlled trials with a less stringent intervention did not confirm these effects.^{23, 24} Some experienced clinicians still feel comfortable using emollients in individuals at risk of AE early in life.

5

Cleansing and bathing

Skin hygiene procedures play an important role in the management of AE, especially in infants and young children. Some authors consider alkaline soaps as disadvantageous compared with liquid cleansers with adequate skin surface pH and lipid content.²⁵ Bathing is regarded as generally superior to washing or showering – especially in young children - also with regard to emotional and psychological interactions between infants and parents.^{26,27} The water temperature should not be too high.²⁸ A recent systematic review has shown that daily bathing or showering is not associated with changes in disease severity, but three studies with qualitative analysis found an improvement of itch and IGA by bathing. Showering may be permitted.²⁹

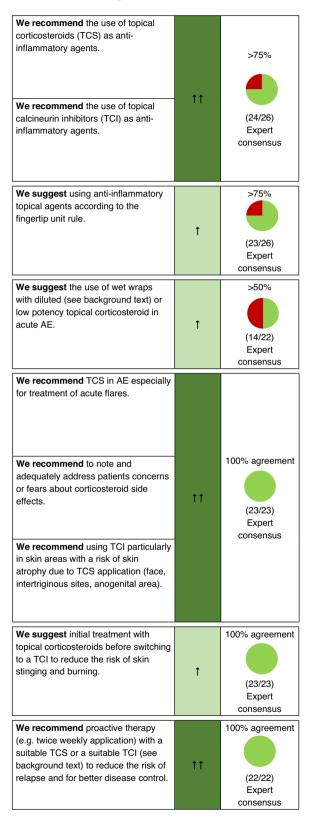
The skin must be cleansed thoroughly, but gently and carefully, to get rid of crusts and mechanically eliminate bacterial contaminants in case of superinfection. Cleansers with or without antiseptics can be used. The duration of action of antiseptics is rather short, and mechanical cleansing is probably more important. Cleansing agents are available in various galenic forms (syndets, aqueous solutions) and should not be too irritating and should not contain strong allergens.^{9,30} The pH values should be between 5 and 6. A small randomized study regarding the frequency of bathing procedures did not show any difference between twice weekly *versus* every day.³¹

In infants, it is easier to perform the first stage of gentle cleansing on the nappy mattress rather than directly in the bathtub. The mechanical component of cleaning helps to remove bacteria from the stratum corneum. Further cleansing is followed by a rapid rinse performed in the bath (27-30°C). The short duration of the bath (approx. 5 min) and the use of bath oils (added for the last 2 min of bathing) are aimed at avoiding epidermal dehydration. Topical emollients are preferentially applied directly after a bath or a shower following gentle drying when the skin is still slightly moist.⁸ It should be emphasized that most bath oils commercially available in Europe are practically free of proteinaceous allergens.³² A recent study found no evidence for a benefit of adding bath additives to standard treatment regimens,³³ while another study found that some bathing additives such as dead sea salt, oatmeal or natural oils, may augment the benefit and reduce the need for or side-effects of pharmacological treatments.³⁴

The addition of antiseptics such as sodium hypochlorite (bleach bath) has proved helpful and is discussed in the chapter 'antimicrobial therapy'.

Adding sodium chloride to bathing water containing oil has been recommended because of its keratolytic and skin moisturizing effect in concentrations up to 5%.³⁵ In adults, higher salt concentrations with the addition of magnesium have been used to mimic the effect of balneotherapy in the dead sea, also together with UV phototherapy³⁶ (see chapter phototherapy).

Anti-inflammatory treatment



Effective topical therapy depends on three fundamental principles: sufficient potency, sufficient dosage and correct application.³⁷ Current approved topical anti-inflammatory therapies are corticosteroids (TCS), calcineurin inhibitors (TCI) and a phosphodiesterase 4 (PDE-4) inhibitor, which is approved in the European Union but not yet available.

The amount of anti-inflammatory topicals applied should follow the fingertip unit rule (see chapter emollient therapy). Topical treatment should ideally be applied on hydrated skin, especially when using ointments ('soak and seal' approach).

Topical anti-inflammatory therapy can be done by two approaches: reactive and proactive management. In the reactive treatment regimen, anti-inflammatory topical therapy is applied to lesional skin only and is stopped or rapidly tapered once visible lesions are cleared or almost cleared. Proactive therapy is defined as a combination of predefined, long-term, antiinflammatory treatment applied usually twice a week to previously affected areas of skin in combination with liberal daily use of emollients on the entire body. Additionally, it is marked by a predefined appointment schedule for clinical examinations.³⁸ The proactive regimen is started after the therapy of the acute flare, when lesions have been successfully treated with regular anti-inflammatory therapy. The duration of proactive management is usually adapted to the severity and persistence of the disease.³⁹

Patients with acute, erosive and oozing lesions, as well as paediatric patients, sometimes do not tolerate standard topical application and may first be treated with 'wet wraps' until the oozing stops. Where clinically superinfected skin is suspected, adding oral antibiotic cover should be considered. Wet wrap medications are highly effective in acute AE and improve tolerance of emollient application. Wet wrap dressings with diluted or lower potency corticosteroids (group II, III, typical dilutions used are 1:3-1:10, usually just for a few days is sufficient) are a safe crisis intervention treatment of severe and/or refractory flares of AE with temporary systemic bioactivity of the corticosteroids as the only reported serious side-effects.^{40–43} Wet wraps can be conducted with topical corticosteroid creams and ointments.⁴⁴ However, this treatment approach is not standardized yet, and the evidence that it is more effective than conventional treatment with topical corticosteroids in AE is not of high quality. Simple or occlusive medications in less sensitive skin areas and for brief time periods may also increase efficacy and speed up lesion resolution.

Topical corticosteroids

Mechanisms of action and efficacy

Topical corticosteroids (TCS) are a first-line anti-inflammatory treatment, typically applied on acutely inflamed skin according to patient needs (pruritus, sleeplessness and new flare).^{45,46} The lipophilicity and the low-molecular weight of TCS allow good

penetration into the skin and binding to a steroid receptor in the cytoplasm. The CS-receptor complex acts as a transcription factor with dual activity, decreasing the synthesis of proinflammatory cytokines and increasing the synthesis of anti-inflammatory mediators.

The potency of topical corticosteroids is grouped according to Niedner from mild (class I) to super-potent (class IV).⁴⁷ This classification is used across Europe and throughout this guideline, except for France, where this classification is similar but in an inversed ranking. The classification used in the US is even different, and recognizes seven groups: from VII (weakest) to I (most potent).

Latest generation TCS with a better risk–benefit ratio are favoured over earlier generation TCS.

Dosage: acute flare, short term and long term

When choosing a TCS, in addition to potency the galenic formulation, patient age and body area to which the medication will be applied should be considered. In children, low-to-moderate potency TCS should be used routinely. Adolescent and adult patients can use potent to very potent TCS under specialist supervision in an acute flare of AE for a short period of time. Potent and very potent TCS are sometimes also used in younger age groups under specialist supervision.

Treatment of the face and especially the peri-orbital region or other sensitive areas (folds and neck) should be restricted to mild-to-moderate TCS (class I and II).⁴⁸

With mild disease activity, a small amount of TCS twice to three times weekly (monthly amounts in the mean range of 15 g in infants, 30 g in children and up to 60–90 g in adolescents and adults, roughly adapted to affected body surface area), associated with a liberal use of daily emollients allows for a good weekly maintenance treatment routine.

Also, patients with moderate or severe AE can benefit from long-term proactive treatment with a moderate to potent TCS. Twice weekly application of fluticasone proprionate or methylprednisolone aceponate (TCS class III) has shown a significant reduction in AE-flare recurrence. Outside of the context of clinical trials, similar experience also exists for other class III and even class II TCS.^{45,46,49}

Safety

For further details on the well-established safety considerations of TCS, see the full version of the guideline.

Monitoring

Monitoring by physical examination for cutaneous side-effects during long-term use of potent TCS is very important.

Itch, which can be assessed by itch Numeric Rating Scale (NRS), is the key symptom for evaluating the response to treatment, and tapering should not be initiated before the itch has largely resolved. In addition to continuous background emollient skin care, one to two applications of TCS per day may be necessary with low- and mid-potency TCS to reduce the itch at the beginning, but one correctly dosed treatment per day is typically sufficient.^{50,51} Dose tapering is usually performed to avoid rebound flares, although no controlled studies have demonstrated its usefulness. Tapering strategies consist of switching to a less potent corticosteroid or keeping a more potent one while reducing the frequency of application (intermittent regimen). The most constructive way to spare corticosteroids and avoid corticosteroid-related side-effects is to start the antiinflammatory treatment early and use them intensively during the acute flares.³⁷

Combination with other treatments

The combination of TCS with topical calcineurin inhibitors (TCI) at the same site does not seem to be useful. At least in paediatric patients with severe AE, the efficacy and safety profile of pimecrolimus cream 1% combined with fluticasone were similar to that of fluticasone alone.⁵² Treating sensitive body areas such as the face (with predeliction to skin thinning) with TCI while treating other affected body areas with a TCS is a common practice but class I and II TCS can be used equally effectively on the face and neck for acute flares. Initial treatment with TCS may be considered in patients with acute flare to minimize TCI site reactions (stinging and burning).³⁹

Special considerations

Patient fear of side-effects of corticosteroids (corticophobia) is quite common and should be recognized (e.g. by TOPICOP score⁵³) and adequately addressed to improve adherence and avoid undertreatment.^{54–56} In pregnancy and lactation, lower potency TCS should be used where possible (see chapter pregnancy, breastfeeding and family planning).

Topical calcineurin inhibitors

Mechanisms of action and efficacy

Two topical calcineurin inhibitors (TCI) (tacrolimus ointment and pimecrolimus cream) are licensed for AE treatment. Pimecrolimus 1% cream and tacrolimus 0.03% ointment are approved in the EU from 2 years of age and above. Elidel[®] cream has additionally been approved in Europe down to 3 months of age. Tacrolimus 0.1% ointment is only licensed in patients age 16 years and above. TCI have an immunosuppressive effect by inhibiting the activity of the phosphorylase enzyme calcineurin and thus inhibiting the activation of T lymphocytes. The transepidermal penetration of TCI is lower than that of TCS.^{57,58} TCI are a first-line therapy for sensitive areas where TCS use is likely associated with side-effects or in areas where TCS has already caused side-effects. The efficacy of both formulations has been demonstrated against vehicle in clinical trials for short-term (3 weeks)^{59,60} and long-term use up to 1 year.^{61,62} The efficacy of long-term monotherapy with tacrolimus ointment has been demonstrated in children and adults.^{63–65} In adults, long-term proactive treatment with 0.1% tacrolimus ointment has shown good effectiveness for flare prevention, similar to class III TCS.⁶⁴ Proactive tacrolimus ointment, but not pimecrolimus 1% cream, has been shown to be safe and effective for up to 1 year in reducing the number of flares and improving quality of life (QoL) in both adults and children.^{66,67} Pimecrolimus 1% cream has been studied in infants and children in a combination regimen with TCS,^{68,69} the latter being given if a flare occurred. Fewer data are available for children under 2 years of age.^{70,71} In children, twice-weekly treatment with tacrolimus 0.03% ointment has been reported to reduce the number of flares and to prolong flare free intervals.

Dosage: acute flare, short term and long term

The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to that of a potent corticosteroid (class III),^{63,64,72} and 0.1% tacrolimus ointment is clearly more effective than 1% pimecrolimus cream.⁶⁵

TCS and TCI can be used in a daily regimen during an acute AE flare. The efficacy of intermittent treatment twice or three times weekly has been investigated in different trials.^{66,67}

Safety

Safety data of both TCI have been reported in many clinical trials and registries, and high-quality long-term safety data have been published from 10-year tacrolimus and 5-year pimecrolimus studies, demonstrating the safety of this anti-inflammatory treatment in daily practice.^{73,74}

None of the TCI induce skin atrophy.^{75,76} This favours their use over TCS in sensitive body areas such as the eyelid region, the perioral skin, the genital area, the axilla region or the inguinal fold, and makes them suitable for long-term management. In addition, the use of TCI may potentially reverse some of the side-effects of TCS when applied on sensitive areas.⁷⁷

After initial concerns from animal studies, resulting in a black box warning from the US Food and Drug Administration (FDA), no convincing evidence for an increased risk of lymphoma has been found in humans.⁷⁸ A long-term safety study over 10 years using tacrolimus ointment 0.03% or 0.1% in children did not show an increased risk of cancer or lymphoma.⁷⁹ The application of TCI is not associated with an increased risk of non-melanoma skin cancer, other malignancies or photocarcinogenicity.^{74,80-84} In a retrospective cohort study with more than 90 000 participants and over 10 years follow-up, no increased risk of basal cell carcinoma or squamous cell carcinoma was observed.⁸⁵ The JOELLE study investigated the risk of lymphoma and skin cancers with the use of TCI and TCS in a very large cohort of paediatric and adult patients and found a positive association. However, given the study design, confounding factors, such as disease severity, have not been ruled out.⁸⁶ A

recent paediatric prospective observational cohort study (APPLES, n = 7954) found no significant association between regular tacrolimus use and lymphoma risk over a 10-year follow-up period. Nevertheless, given that the long-term oral use of ciclosporin (calcineurin inhibitor) is associated with an increased photocarcinogenicity risk in solid organ transplant patients, exposure of the skin to sunlight should be minimized and effective UV protection through the use of sunscreens and appropriate clothing should be recommended in all patients using TCI. Furthermore, the combined use of TCI and photo-therapy should be avoided.⁸⁷

Clinicians should be aware of the black-boxed warning on the use of TCI inhibitors and may discuss this with patients to improve adherence, even if observational studies have not found a convincing association between long-term TCI use and cancer development.⁷⁹

Monitoring

Monitoring by physical examination for cutaneous side-effects during long-term treatment with TCS and TCI is important (also see above).

Special considerations

Although TCI are not approved in pregnancy and lactation (see chapter pregnancy, breastfeeding, family planning), off-label use in pregnancy and lactation is possible as there is no teratogenic potential reported for the entire substance class.⁸⁸

Topical phosphodiesterase 4 inhibitors

Mechanisms of action and efficacy

The topical phosphodiesterase 4 (PDE-4) inhibitor crisaborole is approved for treatment of mild-to-moderate AE in patients 2 years of age and older in the United States, Canada, Australia, Israel and Hong Kong. Crisaborole was approved in the European Union in 2020 but is not commercialized in the European market. Therefore, no recommendations are made.

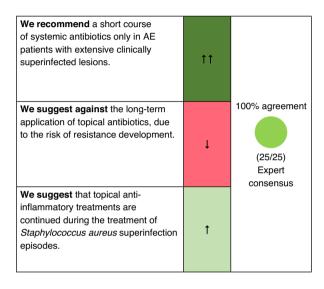
Upcoming topical treatment

Upcoming topical therapies include several topical janus kinase (JAK) inhibitors. First, promising phase II clinical trial data with the topical JAK inhibitor tofacitinib have been published.⁸⁹ Despite these promising results, the clinical development programme of tofacitinib has been stopped. Delgocitinib has been approved for use in AE in Japan.^{89,90} In a 4-week study, the selective JAK-1 and JAK-2 inhibitor ruxolitinib showed a similar or even higher efficacy in mild-to-moderate AE compared with triamcinolone cream (group III TCS) and has recently been approved in the United States.⁹¹ Other JAK inhibitors with similar or different selectivity (brepocitinib) are in the pipeline for topical therapy, but none is currently licensed in Europe.

We suggest treatment with topical		100% agreement
antiseptic drugs - including sodium		
hypochlorite 0.005% baths - in patients		
with a history of recurrent skin	1	
infections.		(24/24)
		Expert
		consensus

Antimicrobial treatment

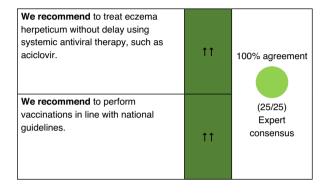
Antibacterial treatment



The prevalence of Staphylococcus aureus (SA) colonization among patients with AE is typically above 80% for lesional skin and 40% for nonlesional skin versus 10% in healthy individuals, but this depends largely on the culture methods used. The density of the colonization correlates with the disease severity.⁹² Topical corticosteroids and calcineurin inhibitors reduce the colonization rate of SA in AE. Although AE patients are prone to SA skin infections, most AE patients colonized by SA do not show overt signs of infection (i.e. weeping, honey-coloured crusts and pustules). Clinical signs of skin inflammation during AE flares may overlap with signs of skin infection, making the diagnosis of skin infection per se challenging.93 Bacterial swabs are commonly unhelpful, as they do not alter the treatment approach, unless the patient is infected with a resistant bacterial species. SA is a major trigger of AE flares, but its role in the development of AE is still debated. There are a number of mechanisms through which SA can drive eczematous inflammation, including the release of superantigen toxins, which enhance Tcell activation of superantigen-specific and allergen-specific T cells, the expression of IgE antistaphylococcal antibodies and increased expression of IL-31 which leads to pruritus and subsequent scratching.^{93,94} Scratching favours binding of SA to the skin, and the increased amount of SA derived ceramidase

aggravates the skin barrier defect. Moreover, superantigen production increases the expression of alternative glucocorticoid receptors that do not bind to topical corticosteroids, which leads to treatment resistance.⁹⁵ Biofilm formation by AE-associated staphylococci most certainly also plays a major role in the occlusion of sweat ducts and leads to inflammation and pruritus.⁹⁵

Antiviral treatment



Viral infections, including herpes simplex, varicella zoster, molluscum contagiosum, smallpox and coxsackie viruses, occur more frequently in AE patients than in healthy individuals, with a tendency to disseminated, widespread disease.⁹⁶

Eczema herpeticum (EH), a disseminated herpes simplex virus (HSV) infection, is a potentially serious complication of AE that requires immediate medical action. Patients, mostly children, present with disseminated vesicles, fever and lymph-adenopathy and can develop complications such as keratoconjunctivitis, meningitis and encephalitis. Predisposing factors of first episode of EH or recurrent EH are early onset and severe or untreated forms of AE with high IgE levels and atopic comorbidities (extrinsic AE). Pretreatment with topical corticosteroids or calcineurin inhibitors is not associated with an increased risk of developing EH. There is no evidence to recommend discontinuation of topical anti-inflammatory treatments during an EH outbreak.⁹⁷ Mainstay of EH therapy is systemic treatment with aciclovir or valaciclovir.⁹⁸ Treatment should be started immediately once the clinical diagnosis is made.³

Varicella-zoster virus (VZV) infection in an immunocompetent child is usually a mild, self-limiting disease. This infection is, however, known to facilitate secondary local or systemic bacterial infection and is a particular concern in children with AE. Earlier studies demonstrated the safety and efficacy of VZV vaccination in these children, who appear to benefit from this vaccination.⁹⁹ Moreover, in children with AE, the immune response to VZV vaccine is comparable to that in healthy children.¹⁰⁰ Therefore, parents of atopic children should be encouraged to fully immunize their children depending on specific local guidelines.

Molluscum contagiosum virus (MCV) infection is in general benign and self-limiting but frequent in patients with severe AE. A large variety of topical treatments have been reported such as cantharidin, potassium hydroxide, tretinoin cream and topical cidofovir.¹⁰¹ Physical therapies, including cryotherapy and curettage, are also effective, but not always well tolerated in paediatric patients and usually unnecessary given the self-limiting nature of MCV infections.¹⁰² Topical treatment of AE with TCS should be continued during MCV infection.

Eczema coxsackium (EC) is a disseminated form of coxsackie virus infection mostly occurring in children with active AE lesions.¹⁰³ The coxsackie virus A6 strain leads to atypical disease manifestations, which are classified as (i) a diffuse form (lesions extended to the trunk), (ii) an acral form (lesions with a mainly acral distribution) or (iii) eczema coxsackium (disseminated lesions on preexisting eczematous areas).¹⁰⁴ This rash may be confused with bullous impetigo or eczema herpeticum. Symptomatic treatment includes topical corticosteroids and wet wrap therapy.^{105,106}

Regional vaccination programmes should be followed by all AE patients as recommended. The denial of vaccination because of diagnosed AE is a misconception possibly leading to fatal consequences.

Antifungal treatment

We suggest topical or systemic anti-		>95%
fungal therapy in some patients with		
AE, mainly in those suffering from the		
"head and neck" variant of AE and	1	
with demonstrated IgE-sensitization to		(23/24)
Malassezia spp.		Expert
		consensus

Despite its role as a commensal on healthy human skin, Malassezia spp. is attributed a pathogenic role in AE, as it may interact with the local skin immune response and barrier function. Through a deficient skin barrier, Malassezia spp. may activate keratinocytes and dendritic cells causing secretion of a range of proinflammatory cytokines including IL-4, IL-13 and IL-17.107-109 The most common class of antifungal drugs prescribed for AE patients are azoles, such as ketoconazole and itraconazole, which also have some antiinflammatory properties.¹¹⁰ Due to a better benefit:side-effect ratio, imidazole derivates (fluconazole or itraconazole) should be prescribed instead of ketoconazole for systemic treatment. In summary, antifungal treatment with either topical ketoconazole or ciclopiroxolamine or systemic itraconazole or fluconazole can be considered for those patients who suffer from head-neck dermatitis, particularly for those who are characterized by clear IgEsensitization to Malassezia spp.

Antipruritic treatment

Itch is the most important clinical symptom in AE with particular impact on emotional dimensions of perception as compared with other pruritic dermatoses. Most drugs successfully used in AE patients, because they are targeting the inflammation, will also have a measurable effect on the itch. Only a limited number of studies have specifically assessed the antipruritic effect of treatment modalities in AE. The management of itch in AE requires a multidimensional approach that treats itch itself but also the contributing factors, such as dry skin and skin inflammation.

Antipruritic effect of anti-inflammatory treatment

Anti-inflammatry agents, whether topical or systemic, reduce skin lesions and significantly relieve itch. Although topical corticosteroids do not act as direct antipruritic agents,¹¹¹ several studies have described the anti-inflammatory effect of topical corticosteroids in AE, in which pruritus was one parameter among others studied.¹¹²

Topical calcineurin inhibitors relieve pruritus significantly in AE. Itch is completely relieved after the first days of treatment in both adults and children. Topical calcineurin inhibitors appeared to significantly reduce AE itch by 36% compared with vehicle application.112

The systemic anti-inflammatory agent dupilumab showed high effectiveness in reducing itch in AE patients.^{113–116} Similar data exist for other systemic drugs recently licensed for AE treatment, such as tralokinumab, abrocitinib, baricitinib and upadacitinib (see chapters biologics and JAK-Inhibitors).^{117–120}

Antipruritic treatment

Polidocanol

We cannot make a recommendation		>75%
on the use of polidocanol in itch		
treatment in AE.		
	0	
		(16/17)
		Expert
		consensus

Topical antihistamines

We recommend against topical		>75%
antihistamines in itch treatment in AE.		
	ĻĻ	
		(17/18) ¹
		Expert
		consensus
11 Abstention		-

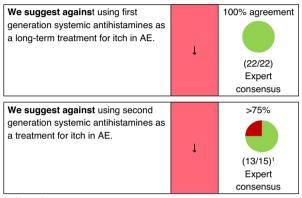
UV therapy

We suggest UV therapy (both		>75%
narrowband UVB and UVA1) for the		
treatment of itch in AE.		
	1 1	
Also see phototherapy chapter		(17/19) ¹
		Expert
		consensus

¹2 Abstentions

UV phototherapy relieves pruritus in AE, which has been demonstrated in several studies. A systematic review of 19 RCTs suggests that narrowband UVB and UVA1 are the most effective forms of phototherapy in the treatment of AE, including reduction in itch intensity.¹²¹ A recent study by Jaworek *et al.*¹²² documented that narrowband UVB reduces itch in AE patients significantly better than ciclosporin.¹²² There are no data specific to using UV phototherapy to treat itch in AE patients that would lead to recommendations that would differ from the general recommendations for using UV phototherapy in the treatment of AE.

Systemic antihistamines

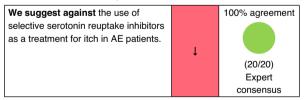


¹1 Abstention

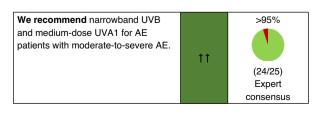
Antihistamines (AH) have been used for decades in an attempt to relieve pruritus in patients with AE. However, only a few randomized controlled trials have been conducted and the majority of them showed only a weak or no effect in decreasing pruritus.^{123–131} A recent Cochrane review did not find consistent evidence that H1 AH treatments are effective as 'add-on' therapy for AE when compared with placebo.¹³² The certainty of evidence for this comparison was of low to moderate quality.¹³²

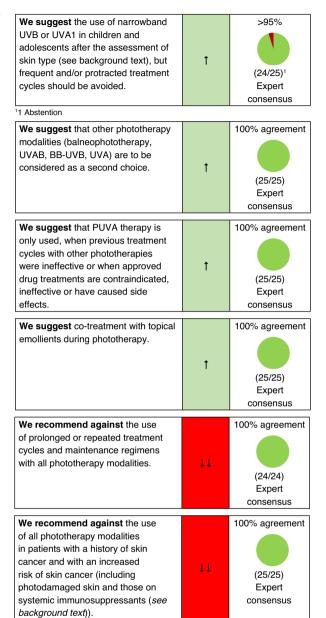
Especially, the first generation of systemic AH may affect sleep quality and reduce rapid eye movement (REM) sleep. Therefore, regular long-term use of sedating antihistamines is not recommended.^{133–135}

Selective serotonin reuptake inhibitors



Phototherapy and photochemotherapy





Efficacy of different photo(chemo)therapy modalities in clinical trials

Photo(chemo)therapy can be used in patients with moderate-tosevere AE recalcitrant to topical therapy. Background information on photobiology, UV modalities and practical aspects can be found in Appendix I in the full version of the guideline. Further information on the systematic review of Garritsen *et al.* is found in the full guideline version.¹²¹ We must, however, emphasize that the use of phototherapy for AE is largely empiric and based on relatively few evidence-based data. There is a clear need for further research on the effectiveness and safety of phototherapy in AE, given that it is frequently used in AE patients.¹³⁶

Safety of different photo(chemo)therapy modalities in clinical trials

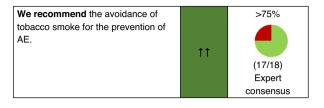
It is evident that our current knowledge on the safety of phototherapy in patients with AE is poor because there are no data from RCTs or registries enrolling large patient cohorts and with prolonged follow-up.

The cancerogenic risk of PUVA is well demonstrated in psoriatic patients, and therefore caution is also recommended in AE patients.^{137–139} However, extrapolating the magnitude of the risk observed with PUVA in patients with psoriasis to the risk in patients with AE is not always correct because psoriatic patients (historically) may have been treated more often with immunosuppressants and / or mutagenic drug therapies.

In patients who use systemic immunosuppressants, especially ciclosporin and azathioprine, phototherapy is not recommended based on their risk of co-carcinogenicity (see chapter conventional systemic drugs).¹⁴⁰ There are few papers available on combination therapy and long-term safety in psoriatic patients^{141,142}; no papers were found specifically for AE (see separate Appendix I of the full version of the guideline).

We recommend to identify individual >75% trigger factors in patients with AE. to avoid these in the future, with the aim of prolonging remission or clearance. 11 (16/17)Expert consensus We recommend to avoid pollen, >75% house dust mite and animal dander as much as possible to prevent exacerbations of AE in sensitized 11 (14/15) patients with a clear history of skin exacerbation. Expert consensus There is no need to restrict normal >75% everyday physical activity in patients with AE. Statement (17/19)Expert consensus We recommend avoiding irritant >75% clothing (e.g. wool with coarse fibers) to prevent an exacerbation of AE in patients with sensitive skin. 11 (16/17)Expert consensus 100% agreement We suggest that patients with AE learn strategies to cope with stress (e.g. educational programmes). Î In selected cases, counselling or (16/16)psychotherapy is suggested. Expert consensus

Avoidance techniques in atopic eczema



House dust mite avoidance

House dust mite (HDM)-related flares may occur in AE patients. Some house dust mite allergens identified by specific IgE or skin prick testing are enzymatically active compounds, which can destroy the cutaneous permeability barrier and may evoke the development of eczematic inflammation in sensitized atopic individuals.

The evidence on HDM avoidance techniques in the prevention of atopic flares is somewhat controversial.^{143–145} Measures to reduce exposure include mattress encasing, the use of adequate indoor ventilation (filter, well-aeration), and the avoidance of wall washing on high temperature.³⁷ HDM, a common indoor allergen occurring in dust, may be reduced by cleaning regularly. Complete eradication by encasing, for example, is not possible.

Animal dander avoidance

When allergies to furry animals are evident, their avoidance is recommended.³⁷ Exposure to cat allergens in particular may be a risk factor for developing inflammatory skin lesions and respiratory symptoms in sensitized patients with AE.¹⁴⁶ There may be an exception for dogs due to a suggested general protective effect of dog-keeping in the development of AE.¹⁴⁷

Exercise/perspiration/physical activity

In AE patients, heat and excessive sweating are one of the main factors reported to exacerbate itch.¹⁴⁸ When excessive sweat is left on the skin, it can lead to occlusion of the sweat pores and formation of keratin plugs which in turn may cause local inflammation and itch. Some of the components of sweat include histamin, antimicrobial peptides and proteases which can induce itch. Sweat can also facilitate the penetration of allergens through the defective atopic skin barrier leading to mast cell degranulation.^{149,150} As sweat is important for skin homeostasis, it is not possible to avoid sweating completely. However, it should be washed off with consistent application of emollients as soon as possible to avoid inducing itch. The evidence concerning physical activity as a trigger for AE is conflicting and incomplete.¹⁴⁸ Although physical activity often leads to sweating, it is important for both physical and mental health, and AE patient should not be advised to avoid it.

Clothing

In patients with AE, certain fabrics such as wool can cause a tingling sensation, skin irritation and itch. The evidence is not completely clear on which fabrics to recommend and which to avoid. Clothing-related exacerbation can be subjective.¹⁵¹ There is no evidence from high-quality studies that certain fabrics decrease the severity of AE.^{151,152} In general, textiles with course fibres, such as certain wool garments and occlusive clothing leading to overheating, should be avoided. Otherwise, the choices of clothing should be based on individual preferences. Most AE patients tolerate silk and cotton well, whereas contact with wool is frequently irritating.

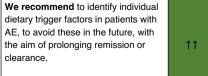
Psychological stress

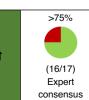
There is good evidence that AE is associated with depression, anxiety and reduced QoL.^{153,154} It is difficult to investigate whether the psychological stress is a cause or consequence of the AE exacerbation, and in many cases, it is probably both. There is a positive correlation between maternal stress and offspring AE.^{155,156} Although evidence from larger studies is lacking, patients report that stress induces itch and flaring of the disease^{157,158} (see chapter psychological intervention).

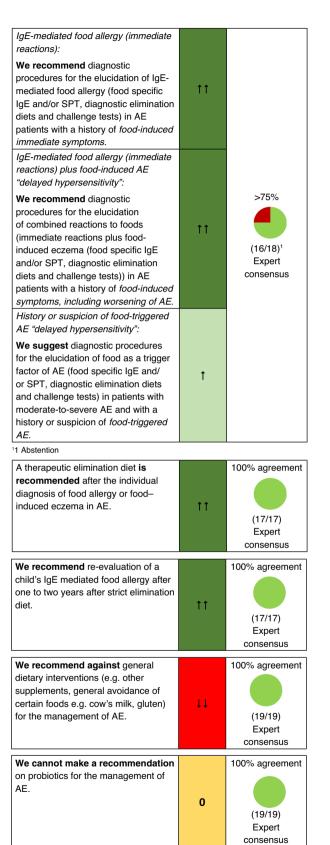
Tobacco smoke

The association of AE with active smoking was found to be significant in a meta-analysis (OR 1.87, 95% confidence interval 1.32–2.63). This association remained significant when looking at only children, only adults and by geographic region. Moreover, the effect of exposure to passive smoke on AE flares is small but also significant (OR 1.18, 95% confidence interval 1.01–1.38). Passive smoke was associated with the prevalence and severity of AE both in children and in adults.¹⁵⁹ The results of a recent registry study of 908 patients with atopic eczema suggest that the intensity of lesions and the Patient Global Assessment Score (PGA) were higher in smoking patients (n = 352) than in non-smoking patients (n = 556). However, physician-assessed disease severity (oSCORAD and EASI scores) did not differ between smokers and non-smokers in this study.¹⁶⁰

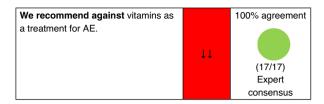
Dietary interventions in atopic eczema







© 2022 The Authors. Journal of the European Academy of Dermatology and Venereology published by John Wiley & Sons Ltd on behalf of European Academy of Dermatology and Venereology.



Food allergens, pre- and probiotics

Food allergy has been documented in approximately one-third of children with moderate–to-severe AE.^{161,162} Among food allergens, cow's milk, hen's egg, peanut, soya, nuts and fish are most frequently responsible for immediate-type food allergy and AE exacerbation in young children, with age-dependent variations in causally incriminated food.¹⁶³ In older children, adolescents and adults pollen-associated food allergy should also be taken into account.^{164–166}

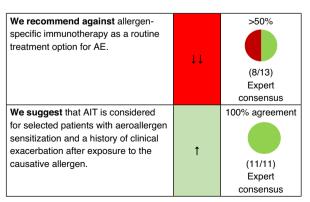
For further details on response patterns to food allergens, see the full version of the guideline.

Pre- and probiotics and dietary supplements

Probiotics such as lactobacillus mixtures have been studied in AE and have been shown to induce improvement in some settings.¹⁶⁷ Other studies failed to show significant effects.^{168,169} In a study with 800 infants, the effect of a prebiotic mixture was investigated and found to have beneficial effects in preventing the development of AE.¹⁷⁰ A recent Cochrane review identified 39 randomized controlled trials involving 2599 randomized participants.¹⁷¹ The authors concluded that compared with no probiotic, currently available probiotic strains probably make little or no difference in improving patient-rated eczema symptoms. However, in 2020, the systematic review by Tan-Lim *et al* found that certain probiotic preparations (*Bifidobacterium animalis subsp lactis* CECT 8145, *Bifidobacterium longum* CECT 7347, and *Lactobacillus casei* CECT 9104; *Lactobacillus casei* DN-114001) show benefit in reducing allergic symptoms in paediatric AE.¹⁷²

A systemic review on dietary supplements including fish oil, vitamin D or vitamin E came to the conclusion that there is no convincing evidence of the benefit of dietary supplements in AE.¹⁷³

Allergen-specific immunotherapy



The cause of symptoms in allergic patients is that the sensitized individual reacts with an allergic immune response to an otherwise harmless allergen. The aim of allergen-specific immunotherapy (AIT) is to theoretically cure allergic diseases. The role of allergen sensitization in AE pathogenesis has been investigated but remains to be fully elucidated. Inflammatory processes seem to be mediated by both an immediate-type reaction, initiated by the internalization of the complex IgE specific/allergens from epidermal dendritic cells, and a delayed T-cell reactivity, characterized by a Th2 inflammatory pattern.¹³³

One of the most important allergen sources in AE are HDM due to the perennial exposure. Recent studies have also focused on the role of pollen allergens as a trigger for AE flare-ups.

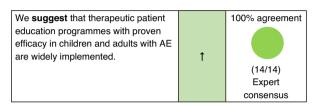
AIT consists of administering increasing doses of allergen to modulate the response and promote peripheral immune tolerance mechanisms. AIT induces a shift from a Th2 to a Th1 immune response pattern, a decrease of mediator release from mast cells and the production of blocking antibodies IgG4.

Complementary medicine

We recommend against acupuncture as standard therapy for AE.	ŢŢ	100% agreement (13/13) Expert consensus
We recommend against phytotherapy as standard therapy for AE.	ŢŢ	100% agreement (14/14) Expert consensus
We recommend against blood autologous serum as standard therapy for AE.	ŢŤ	100% agreement (12/12) Expert consensus
We recommend against Chinese herbal medicine as standard therapy for AE.	ŢŤ	100% agreement (12/12) Expert consensus
We cannot make a recommendation with respect to alpine climate therapy for AE.	0	>75% (11/12) Expert consensus

Complementary medicine describes a wide variety of healthcare practices used alongside standard medical treatment. These include alternative health approaches such as traditional Chinese medicine, acupuncture, autologous blood therapy, phytotherapy and highaltitude alpine climate. Overall, the evidence to support any of these treatments for AE was not strong enough. Further details on our critical appraisal are found in the full version of the guideline.

Psychological and educational interventions



Psychological and emotional factors as well as psychodynamic structures within the family are well-known elements that may influence the clinical course of AE.¹⁷⁴ Stress can elicit severe exacerbations of the disease and perpetuate the itch-scratch cycle. Anxiety or depression are acknowledged comorbidities in AE patients.¹⁵⁴ Furthermore, poor QoL and adherence to treatment are key issues in these patients.¹⁷⁵ As a multidimensional phenomenon, low treatment adherence is influenced by factors such as the disease itself, its chronicity but also by the patient's beliefs and characteristics. It can be improved by introducing specific strategies after understanding the patient's adherence pattern.¹⁷⁵ Therapeutic patient education (TPE) programmes were originally designed to enable people with chronic diseases to manage their illness (increasing autonomy and decreasing medical complications). They can help patients and their families to better understand and accept their disease and cope with treatment in order to improve QoL and treatment adherence. The aim of TPE is not simply to provide information by leaflets, but entails the transfer of skills (e.g. disease self-management strategies, knowledge of treatments, relaxation and behavioural therapy techniques) from a trained healthcare professional to the patient or their parents.¹⁷⁶ Additionally, as TPE is patientcentred holistic care, it should facilitate a better partnership between doctors and their patients/caregivers. TPE can also help restore family dynamics. Parents with negative treatment experiences in the past and poor coping abilities regarding scratch control are likely to benefit most from TPE programmes.¹⁷⁷

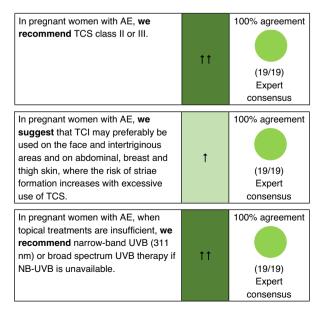
High-quality TPE programmes should ideally be evidencebased, tailored to a patient's needs, taking into account the individual educational and cultural background (rather than being standardized in form and content). It should also have welldefined content and activities that are provided by an interdisciplinary healthcare team.¹⁷⁸

There is also some evidence for nurse- and psychologist-led programmes as well as e-health education. For further details see the full version of the guideline. Structured interdisciplinary high-quality education programmes should be implemented regardless of the severity of AE. They can improve the efficacy of topical treatment and be particularly helpful in evaluating the next treatment steps, like the necessity of introducing systemic treatments. Psychological interventions, for example autogenic training, relaxation, cognitive-behavioural therapy, habit reversal and behavioural therapies have a positive effect on different aspects of AE.

Pregnancy, breastfeeding and family planning

The current ethical framework of GCP guidelines deems it unethical to perform clinical trials in pregnant women. Therefore, there is no high-level evidence on efficacy and safety in this patient population. AE is the most common general skin disease in pregnancy. AE may either (i) worsen in women with a chronic condition, or (ii) may be reactivated in patients with a past AE history or (iii) may occur in women with no AE history (atopic eruption of pregnancy, AEP). Worsening of AE is mostly reported during the second and third trimesters, while AEP typically occurs during the first trimester.⁸⁸ There are no major clinical differences between classical AE worsening and AEP. Physiological skewness of the immune system towards a Th2dominated response during pregnancy as well as physical and psychological stress during this period may contribute to AE worsening during pregnancy. Little is known about treatment patterns during pregnancy, but patients and caregivers tend to reduce the use of topical and systemic therapies to avoid presumed harm to the fetus.¹⁷⁹ Consequently, undertreatment of AE during pregnancy may lead to serious QoL impairment but also to complications such as eczema herpeticum or staphylococcus aureus skin infections, and should therefore be avoided.

Pregnant women



In pregnant women with AE who are candidates for systemic treatment we suggest ciclosporin.	Ť	100% agreement (14/14) Expert consensus
In pregnant women with AE who are being treated with azathioprine and still need a systemic treatment we suggest continuing azathioprine.	t	100% agreement (14/14) Expert consensus
In pregnant women with AE, we recommend against long term use of systemic corticosteroids - as we do in all AE patients.	ţţ	100% agreement
In pregnant women with AE, we suggest prednisolone only as short term rescue therapy for acute flares.	Ť	(16/16) Expert consensus
In pregnant women with AE, we recommend against the use of abrocitinib, baricitinib, upadacitinib, methotrexate and mycophenolate.	ţţ	100% agreement (12/12) Expert consensus
In pregnant women with AE, we cannot make a recommendation regarding the use of dupilumab during pregnancy due to the current lack of clinical data.	0	100% agreement (16/16) Expert consensus

First-line treatments

Emollients. Basic emollient therapy is key in the treatment of AE also during pregnancy and must be proposed to pregnant women with AE as a basic daily therapy. There is no firm evidence on which emollient should be used, but using one with a high lipid content and as few potentially harmful agents as possible is recommended. Using emollients in a wet wrap technique is encouraged.³

TCS. Reactive or proactive use of TCS class II or III is recommended. A Cochrane systematic review updated in 2015 including 14 studies (5 cohort and 9 case–control studies) with 1 601 515 study subjects has examined the risk of TCS use in pregnancy. Overall, it has been deemed safe, with no causal associations between maternal exposure to TCS of all potencies and pregnancy outcomes including mode of delivery, congenital abnormalities, preterm delivery, fetal death, and low Apgar score, although the use of very potent topical corticosteroids may be associated with low birthweight.¹⁸⁰ Proactive, twice weekly TCS application as maintenance therapy is regarded as safe, but caution is recommended when using potent TCS over large body surface areas, or sensitive

areas such as breast and thigh skin, on a more regular basis. Some experts suggest that class IV may be used as rescue therapy, or over longer periods on limited skin areas, but this is controversial. Fluticasone propionate should be avoided as it is the only TCS that is known not to be metabolized by the placenta.⁸⁸

TCI. Reactive and proactive use of TCI may be preferable on the face and intertriginous areas, and on abdominal, breast and thigh skin, where the risk of striae formation increases with excessive use of TCS.

Antiseptics. Antiseptics, except triclosan, may be used by pregnant women if clinically needed to prevent recurring skin infections, but are not recommended as a general routine measure.

UV phototherapy. Therapy with narrowband UVB (311 nm) and broad-spectrum UVB does not impose a risk to the fetus in pregnant woman. However, oral psoralen should not be used preconceptionally (3 months) or in pregnant women.

Second- and third-line treatments

Second- and third-line treatments are recommended in pregnant women with AE who are inadequately controlled with TCS class II or III.

Systemic corticosteroids should not be used in the long-term in AE in general and even more so not during pregnancy, as it is associated with an increased risk of fetal complications, including gestational diabetes.¹⁸⁰ Only short courses of prednisolone (maximum 0.5 mg/kg/d) may be used with strict indication.

Ciclosporin may be used off-label in severe uncontrolled AE during pregnancy if topical anti-inflammatory treatment alone or in combination with UV treatment failures, and there is a clear need for better long-term disease control. However, extra attention should be given to the renal function and blood pressure of the mother. There is no evidence of teratogenicity. Ciclosporin crosses the placenta¹⁸¹ and should not be used during pregnancy, unless the potential benefit to the mother justifies the potential risk to the fetus.

AZA may be used off-label in pregnant women with severe uncontrolled AE who are already receiving this treatment at the time of conception. There is no evidence for teratogenicity from studies with patients with inflammatory bowel diseases. Closely consulting an experienced obstetrician when prescribing this drug is strongly recommended.⁸⁸

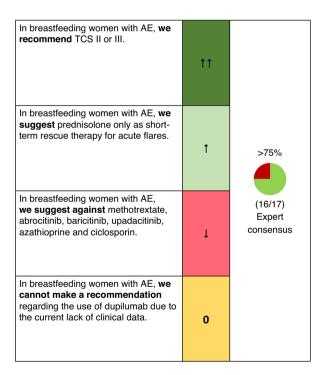
MTX and mycophenolate mofetil are teratogenic and therefore strictly contraindicated during pregnancy. We cannot recommend any of the novel systemic medications, as there are currently no clinical data available to inform about any potential drug-associated risks. Pre-clinical data do not indicate that there would be a teratogenic potential of dupilumab or tralokinumab if given during pregnancy.

Abrocitinib, baricitinib and upadacitinib are contraindicated during pregnancy according to label. There are no clinical data but single case reports supporting its safety in pregnant women, but teratogenic effects have been described in animal models.

Antihistamines are of limited efficacy in AE (see chapter antipruritic treatment). In case of need, loratadine should preferentially be used because of the broad experience with this drug in pregnant women.

Due to lack of experience with crisaborole during pregnancy, this drug should not be used preconceptionally, in pregnancy or during lactation.

Specific consideration for breastfeeding women

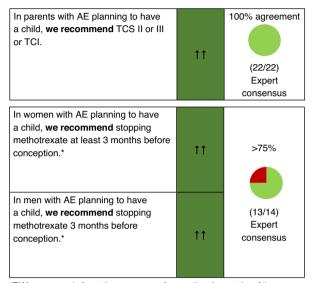


TCS and TCI: No studies have examined the safety of TCS and TCI use during lactation but no harmful effect is suspected. Nevertheless, it is recommended to apply the topical treatment in the nipple region immediately after nursing the child, to allow the drug to be absorbed into the skin before the next feeding.⁸⁸

Systemic corticosteroids: Treatment with a short course of a systemic corticosteroids during lactation is safe, since <0.1% of the mother's ingested dosage is secreted into breastmilk.

MTX, AZA, ciclosporin and JAK inhibitors are secreted in breastmilk and may induce immunosuppression in the neonate. MTX, AZA, ciclosporin and JAK inhibitors are generally not recommended for lactating mothers.⁸⁸

Family planning



*EMA recommends 6 months as a means of precaution, the practice of the guideline group differs from this.

Preconception recommendations for women

TCS and TCI: Although the literature on this subject is very sparse, topical AE therapies in women wishing to conceive can be used without concern.

MTX: Local labels in different countries suggest a contraindication range spanning from 1 month to 6 months before conception. The European Medicines Agency (EMA) recommends 6 months as a means of precaution. The practice of the guideline group differs from this, and we recommend stopping methotrexate 3 months before conception.

Preconception recommendations for men

TCS and TCI: Although the literature on this subject is very sparse, topical AE therapies in men wishing to father a child can be used without concern.

Ciclosporin may be used in the treatment of AE in men at the time of conception, as there is no evidence for harm or decreased fertility.

MTX: Following the European S3-guideline on systemic treatment of psoriasis vulgaris, a 3-month MTX pause prior to conception is recommended. However, (inadvertent) exposure beyond this time does not justify termination of pregnancy, because there is no evidence of male teratogenicity.⁸⁸

AZA and baricitinib: there is no contraindication for the use of AZA and baricitinib in men wishing to father a child.

Considerations for paediatric and adolescent patients

AE may appear during the first months of life, and most patients develop the condition before the age of 5 years. Around 60% of children outgrow AE in some cases. However, significant numbers present with either AE or hand eczema as adults.¹⁸²

Severe early disease and a family history of AE may predict a more persistent course.¹³

During infancy (0–2 years), the predeliction areas are the cheeks, head, trunk, and extensor surfaces of the extremities, although flexural involvement is also common, which becomes an even more prominent feature during later childhood.

The first clinical signs often appear on the cheeks in form of erythematous, oozing, crusted plaques. The symptoms may then generalize and spread to the scalp, forehead, trunk and limbs. Centrofacial pallor along with spared area of the nose and paranasal skin cause the 'headlight sign' appearance. The diaper area is also usually intact in infancy. The facial symptoms usually decrease by the end of the first year.¹⁸³

Prematurity causes barrier dysfunction with higher transepidermal water loss (TEWL) and increased percutaneous absorption of chemicals. This is an important factor when planning local treatment dosage, body area, and duration. Infants are more susceptible to percutaneous toxicity. Their high surface area-to-volume ratio, immature drug metabolism systems, and decreased subcutaneous fat stores increase the absorption potential of the skin, while decreasing the volume of distribution of a drug or toxin. In full-term infants, skin barrier development continues during the first year of life.

Bathing an infant provides important psychological benefits between parent and child. Bathing of infants with AE should be brief to maintain the microbial flora, which changes with age, avoiding harsh soaps and detergents and using bath emollients to aid skin hydration and emollients as soap substitutes to aid barrier function.¹⁸⁴

Wet wraps can be a useful treatment approach where additional hydration of the skin is needed, in particular in young children.⁴⁴

Table 3	Occupations	with an elevated	d risk of hand	d eczema
---------	-------------	------------------	----------------	----------

With mild disease activity, maintenance use of topical corticosteroid twice to three times weekly (monthly amounts in the mean range of 15 g in infants, 30 g in children and up to 60– 90 g in adolescents and adults, adapted to affected body surface area) with a liberal use of emollients do not result in adverse systemic or local effects.¹³

To treat the face of a 3-month-old infant, 1 FTU will suffice. To fully cover an entire leg of a 6-year-old, a 4 FTU dose is used.

TCI may effectively and safely be used as anti-inflammatory agents in the treatment of AE, especially on sensitive skin areas (e.g. face), from age two. The use of TCI in younger children is common.¹³³ Daily application (BID) is recommended during relapses on the affected area, following the FTU rules, while according to the proactive regimen they may also be applied twice a week on the symptom-free areas.¹³ TCI are also used under 2 years of age in many centres.

Occupational aspects

AE can have a negative impact on work life and is associated with a higher risk of hand eczema.	Statement	100% agreement (15/15) Expert consensus
We suggest individual pre- employment counselling regarding choice of profession, including risk assessment, avoidance strategies and protective measures.	Î	100% agreement (23/23) Expert consensus

A number of occupational aspects are relevant to AE patients, as they run a significant risk of developing occupational contact dermatitis. Atopy amplifies the effects of irritant and allergen exposure in several professions such as hairdressers, nurses, metalworkers, mechanics and cleaners, where hand eczema is a very

Job/occupation	Possible sensitizing compounds and atopic eczema triggers
Hairdresser	Hair dyes, perm products, haircare products, rubber auxiliary materials, bleaching agents
	detergents, wet-work, cosmetic preservatives
Beauticians	Acrylics, acrylates, cosmetic preservatives, rubber auxiliary materials, wet-work
Cleaning and housekeeping	Disinfectants, rubber auxiliary materials, abrasives, wet-work
Baker	Flour and grain dust, rubber auxiliary materials, wet-work
Painter	Paints, isocyanates, resins, turpentine, paint pigments, preservatives
Construction and cement worker	Isocyanates, cement, concrete, glues, paints, resins, fibreglass, and metals
Carpenter	Woods
Agricultural worker	Animal particles, disinfectants, plants, rubber auxiliary materials
Florist and gardener	Plants, rubber auxiliary materials, wet-work
Healthcare worker	Latex, disinfectants, rubber auxiliary materials, medications, wet-work
Veterinarian, animal lab worker, zookeeper	Animal particles, disinfectants, rubber auxiliary materials, medications, tools, wet-work
Catering and cooking employees	Detergents, disinfectants, foods, rubber auxiliary materials, wet-work
Wind energy technician	Solvents, glues, paints, epoxy, resins, fibreglass, acids and alkalis, detergents
Mechanic and metal worker	Cutting fluids, coolants, detergents, metals, petroleum products, preservatives

© 2022 The Authors. Journal of the European Academy of Dermatology and Venereology published by John Wiley & Sons Ltd on behalf of European Academy of Dermatology and Venereology. common disease.¹³³ The risk of hand eczema in AE patients is increased about fourfold.¹⁸⁵ Physicians should inform AE patients about the increased risk, and provide good guidance about prophylactic skin protection and irritant/contact allergen avoidance. All dermatologists treating adolescent patients with AE should advise these early on occupational aspects of their skin disease and suitable career choices.¹³³ For further information on impact of AE on work life, see Table 3 and the full version of the guideline.

Strengths and limitations

The vision of this guideline was to provide a comprehensive evidence-based update on all aspects of AE care with high relevance to practising clinicians across Europe. To reflect the latest methodological rigour in guideline development, the formal structure of the guideline document has been changed to follow the structure and style of the EuroGuiDerm guidelines. We assembled a guideline development group (GDG) that included clinical and methodological experts from across Europe, including patients. Our clear conflict of interest policy has created more transparency and was also reflected in the online voting procedures on standardized guideline statements.

While this regulated process of guideline formation has resulted in higher methodolocal rigour, independence, objectivity and quality of the content, we are conscious that the guideline document is already outdated regarding the fastest changing content, in particular the chapter on systemic therapy. However, we plan to update the content of this aspect of the guideline on a regular basis, creating a 'living' guideline for systemic AE therapies.

Acknowledgement

Open Access funding enabled and organized by Projekt DEAL.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

References

- Loden M, Andersson AC, Anderson C et al. A double-blind study comparing the effect of glycerin and urea on dry, eczematous skin in atopic patients. Acta Derm Venereol 2002; 82: 45–47.
- 2 Darsow U, Lübbe J, Taïeb A et al. Position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Dermatol Venereol 2005; 19: 286– 295.
- 3 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.
- 4 van Zuuren EJ, Fedorowicz Z, Christensen R, Lavrijsen A, Arents BWM. Emollients and moisturisers for eczema. *Cochrane Database Syst Rev* 2017; 2: CD012119.
- 5 Boralevi F, Saint Aroman M, Delarue A *et al*. Long-term emollient therapy improves xerosis in children with atopic dermatitis. *J Eur Acad Dermatol Venereol* 2014; 28: 1456–1462.
- 6 Schram ME, Spuls PI, Leeflang MM, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema:

- 7 Akerstrom 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.
- 8 Chiang C, Eichenfield LF. Quantitative assessment of combination bathing and moisturizing regimens on skin hydration in atopic dermatitis. *Pediatr Dermatol* 2009; 26: 273–278.
- 9 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.
- 10 Mengeaud V, Phulpin C, Bacquey A, Boralevi F, Schmitt AM, Taieb A. An innovative oat-based sterile emollient cream in the maintenance therapy of childhood atopic dermatitis. *Pediatr Dermatol* 2015; **32**: 208– 215.
- 11 Angelova-Fischer I, Rippke F, Richter D et al. Stand-alone emollient treatment reduces flares after discontinuation of topical steroid treatment in atopic dermatitis: a double-blind, randomized, vehiclecontrolled, Left-right Comparison Study. Acta Derm Venereol 2018; 98: 517–523.
- 12 Wollenberg A, Schnopp C. Evolution of conventional therapy in atopic dermatitis. *Immunol Allergy Clin North Am* 2010; 30: 351–368.
- 13 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.
- 14 Gelmetti C, Wollenberg A. Atopic dermatitis all you can do from the outside. *Br J Dermatol* 2014; **170**(Suppl 1): 19–24.
- 15 National Institute for Health and Care Excellence. NICE pathways: eczema. Vol. 03.08.2021. 2020.
- 16 Mandeau A, Aries MF, Boe JF et al. Rhealba(R) oat plantlet extract: evidence of protein-free content and assessment of regulatory activity on immune inflammatory mediators. *Planta Med* 2011; 77: 900–906.
- 17 Gueniche A, Knaudt B, Schuck E *et al.* Effects of nonpathogenic gramnegative bacterium Vitreoscilla filiformis lysate on atopic dermatitis: a prospective, randomized, double-blind, placebo-controlled clinical study. *Br J Dermatol* 2008; **159**: 1357–1363.
- 18 Aries MF, Hernandez-Pigeon H, Vaissiere C et al. Anti-inflammatory and immunomodulatory effects of Aquaphilus dolomiae extract on in vitro models. Clin Cosmet Investig Dermatol 2016; 9: 421–434.
- 19 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; 2013: Cd004416.
- 20 Gehring W, Bopp R, Rippke F, Gloor M. Effect of topically applied evening primrose oil on epidermal barrier function in atopic dermatitis as a function of vehicle. *Arzneimittelforschung* 1999; **49**: 635–642.
- 21 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.
- 22 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, e6–830.
- 23 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.
- 24 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.
- 25 Uehara M, Takada K. Use of soap in the management of atopic dermatitis. Clin Exp Dermatol 1985; 10: 419–425.
- 26 Blume-Peytavi U, Cork MJ, Faergemann J, Szczapa J, Vanaclocha F, Gelmetti C. Bathing and cleansing in newborns from day 1 to first year of life: recommendations from a European round table meeting. *J Eur Acad Dermatol Venereol* 2009; 23: 751–759.

- 27 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 (Phila)* 2016; **55**: 176–181.
- 28 Denda M, Sokabe T, Fukumi-Tominaga T, Tominaga M. Effects of skin surface temperature on epidermal permeability barrier homeostasis. J Invest Dermatol 2007; 127: 654–659.
- 29 Hua T, Yousaf M, Gwillim E et al. Does daily bathing or showering worsen atopic dermatitis severity? A systematic review and metaanalysis. Arch Dermatol Res 2020; 313: 729–735.
- 30 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.
- 31 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 (Phila)* 2014; **53**: 677–681.
- 32 Ring J, Mohrenschlager M. Allergy to peanut oil--clinically relevant? J Eur Acad Dermatol Venereol 2007; 21: 452–455.
- 33 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.
- 34 Maarouf M, Hendricks AJ, Shi VY. Bathing additives for atopic dermatitis - a systematic review. *Dermatitis* 2019; 30: 191–197.
- 35 Ludwig G. On the topical effect of sea water tub-baths with and without addition of an oil emulsion. *Zeitschrift fur Haut-und Geschlechtskrankheiten* 1968; **43**: 683–688.
- 36 Dittmar HC, Pflieger D, Schempp CM, Schopf E, Simon JC. Comparison of balneophototherapy and UVA/B mono-phototherapy in patients with subacute atopic dermatitis. *Hautarzt* 1999; 50: 649–653.
- 37 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.
- 38 Wollenberg A, Frank R, Kroth J et al. Proactive therapy of atopic eczema – an evidence-based concept with a behavioral background. J Dtsch Dermatol Ges 2009; 2009: 117–121.
- 39 Wollenberg A, Ehmann LM. Long term treatment concepts and proactive therapy for atopic eczema. Annals Dermatol 2012; 24: 253–260.
- 40 Schnopp C, Holtmann C, Stock S *et al.* Topical steroids under wet-wrap dressings in atopic dermatitis--a vehicle-controlled trial. *Dermatology* 2002; 204: 56–59.
- 41 Gonzalez-Lopez G, Ceballos-Rodriguez RM, Gonzalez-Lopez JJ, Feito Rodriguez M, Herranz-Pinto P. Efficacy and safety of wet wrap therapy for patients with atopic dermatitis: a systematic review and metaanalysis. Br J Dermatol 2016; 177: 688–695.
- 42 Kohn LL, Kang Y, Antaya RJ. A randomized, controlled trial comparing topical steroid application to wet versus dry skin in children with atopic dermatitis (AD). *J Am Acad Dermatol* 2016; **75**: 306–311.
- 43 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.
- 44 Cadmus SD, Sebastian KR, Warren D *et al*. Efficacy and patient opinion of wet-wrap dressings using 0.1% triamcinolone acetonide ointment vs cream in the treatment of pediatric atopic dermatitis: a randomized split-body control study. *Pediatr Dermatol* 2019; **36**: 437–441.
- 45 Hanifin J, Gupta AK, Rajagopalan R. Intermittent dosing of fluticasone propionate cream for reducing the risk of relapse in atopic dermatitis patients. Br J Dermatol 2002; 147: 528–537.
- 46 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. *BMJ* 2003; **326**: 1367–1360.
- 47 Niedner R. Therapie mit systemischen Glukokortikoiden. *Hautarzt* 2001; **52**: 1062–1071.

- 48 Barnes L, Kaya G, Rollason V. Topical corticosteroid-induced skin atrophy: a comprehensive review. *Drug Saf* 2015; 38: 493–509.
- 49 Van Der Meer JB, Glazenburg EJ, Mulder PG, Eggink HF, Coenraads PJ. The management of moderate to severe atopic dermatitis in adults with topical fluticasone propionate. The Netherlands adult atopic Dermatitis-Study group. *Br J Dermatol* 1999; **140**: 1114–1121.
- 50 Queille C, Pommarede R, Saurat JH. Efficacy versus systemic effects of six topical steroids in the treatment of atopic dermatitis of childhood. *Pediatr Dermatol* 1984; 1: 246–253.
- 51 Charman C, Williams H. The use of corticosteroids and corticosteroid phobia in atopic dermatitis. *Clin Dermatol* 2003; **21**: 193–200.
- 52 Meurer M, Eichenfield LF, Ho V, Potter PC, Werfel T, Hultsch T. Addition of pimecrolimus cream 1% to a topical corticosteroid treatment regimen in paediatric patients with severe atopic dermatitis: a randomized, double-blind trial. *J Dermatolog Treat* 2010; **21**: 157–166.
- 53 Stalder JF, Aubert H, Anthoine E *et al.* Topical corticosteroid phobia in atopic dermatitis: international feasibility study of the TOPICOP score. *Allergy* 2017; **72**: 1713–1719.
- 54 Aubert-Wastiaux H, Moret L, Le Rhun A et al. Topical corticosteroid phobia in atopic dermatitis: a study of its nature, origins and frequency. Br J Dermatol 2011; 165: 808–814.
- 55 Lee JY, Her Y, Kim CW, Kim SS. Topical corticosteroid phobia among parents of children with atopic eczema in Korea. *Annals Dermatol* 2015; 27: 499–506.
- 56 Müller SM, Tomaschett D, Euler S, Vogt DR, Herzog L, Itin P. Topical corticosteroid concerns in dermatological outpatients: a cross-sectional and interventional study. *Dermatology* 2016; 232: 444–452.
- 57 Carr WW. Topical calcineurin inhibitors for atopic dermatitis: review and treatment recommendations. *Paediatr Drugs* 2013; 15: 303–310.
- 58 Norris DA. Mechanisms of action of topical therapies and the rationale for combination therapy. J Am Acad Dermatol 2005; 53: S17–S25.
- 59 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.
- 60 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.
- 61 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.
- 62 Meurer M, Folster-Holst R, Wozel G et al. Pimecrolimus cream in the long-term management of atopic dermatitis in adults: a six-month study. *Dermatology* 2002; 205: 271–277.
- 63 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.
- 64 Cury Martins J, Martins C, Aoki V, Gois AF, Ishii HA, da Silva EM. Topical tacrolimus for atopic dermatitis. *Cochrane Database Syst Rev* 2015: CD009864.
- 65 Chen SL, Yan J, Wang FS. Two topical calcineurin inhibitors for the treatment of atopic dermatitis in pediatric patients: a meta-analysis of randomized clinical trials. *J Dermatolog Treat* 2010; 21: 144–156.
- 66 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.
- 67 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.
- 68 Ho VC, Gupta A, Kaufmann R *et al*. Safety and efficacy of nonsteroid pimecrolimus cream 1% in the treatment of atopic dermatitis in infants. *J Pediatr* 2003; **142**: 155–162.
- 69 Eichenfield LF, Lucky AW, Boguniewicz M *et al.* Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and

moderate atopic dermatitis in children and adolescents. J Am Acad Dermatol 2002; 46: 495–504.

- 70 Patel RR, Vander Straten MR, Korman NJ. The safety and efficacy of tacrolimus therapy in patients younger than 2 years with atopic dermatitis. *Arch Dermatol* 2003; **139**: 1184–1186.
- 71 Reitamo S, Mandelin J, Rubins A *et al.* The pharmacokinetics of tacrolimus after first and repeated dosing with 0.03% ointment in infants with atopic dermatitis. *Int J Dermatol* 2009; **48**: 348–355.
- 72 Abędź N, Pawliczak R. Efficacy and safety of topical calcineurin inhibitors for the treatment of atopic dermatitis: meta-analysis of randomized clinical trials. *Postepy Dermatologii i Alergologii* 2019; 36: 752–759.
- 73 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.
- 74 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.
- 75 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.
- 76 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.
- 77 Hong CH, Gooderham M, Bissonnette R. Evidence review of topical Calcineurin inhibitors for the treatment of adult atopic dermatitis. J Cutan Med Surg 2019; 23: 5s–10s.
- 78 Ohtsuki M, Morimoto H, Nakagawa H. Tacrolimus ointment for the treatment of adult and pediatric atopic dermatitis: review on safety and benefits. *J Dermatol* 2018; 45: 936–942.
- 79 Paller AS, Fölster-Holst R, Chen SC *et al.* No evidence of increased cancer incidence in children using topical tacrolimus for atopic dermatitis. *J Am Acad Dermatol* 2020; 83: 375–381.
- 80 Ring J, Barker J, Behrendt H *et al.* Review of the potential photococarcinogenicity of topical calcineurin inhibitors: position statement of the European dermatology forum. *J Eur Acad Dermatol Venereol* 2005; 19: 663–671.
- 81 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.
- 82 Thaci D, Salgo R. Malignancy concerns of topical calcineurin inhibitors for atopic dermatitis: facts and controversies. *Clin Dermatol* 2010; 28: 52–56.
- 83 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.
- 84 Deleuran M, Vestergaard C, Vølund A, Thestrup-Pedersen K. Topical Calcineurin inhibitors, topical glucocorticoids and cancer in children: a Nationwide study. Acta Derm Venereol 2016; 96: 834–835.
- 85 Asgari MM, Tsai AL, Avalos L, Sokil M, Quesenberry CP Jr. Association between topical Calcineurin inhibitor use and keratinocyte carcinoma risk among adults with atopic dermatitis. *JAMA Dermatol* 2020; 156: 1066–1073.
- 86 Castellsague J, Kuiper JG, Pottegard A *et al*. A cohort study on the risk of lymphoma and skin cancer in users of topical tacrolimus, pimecrolimus, and corticosteroids (joint European longitudinal lymphoma and skin cancer evaluation - JOELLE study). *Clin Epidemiol* 2018; **10**: 299– 310.
- 87 Czarnecka-Operacz M, Jenerowicz D. Topical calcineurin inhibitors in the treatment of atopic dermatitis – an update on safety issues. J Dtsch Dermatol Ges 2012; 10: 167–172.
- 88 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.

- 89 Bissonnette R, Papp KA, Poulin Y *et al.* Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. *Br J Dermatol* 2016; **175**: 902– 911.
- 90 Nakagawa H, Nemoto O, Igarashi A, Nagata T. Efficacy and safety of topical JTE-052, a Janus kinase inhibitor, in Japanese adult patients with moderate-to-severe atopic dermatitis: a phase II, multicentre, randomized, vehicle-controlled clinical study. *Br J Dermatol* 2018; **178**: 424– 432.
- 91 Kim BS, Howell MD, Sun K, Papp K, Nasir A, Kuligowski ME. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. J Allergy Clin Immunol 2020; 145: 572–582.
- 92 Totté JE, van der Feltz WT, Hennekam M, van Belkum A, van Zuuren EJ, Pasmans SG. Prevalence and odds of Staphylococcus aureus carriage in atopic dermatitis: a systematic review and meta-analysis. *Br J Dermatol* 2016; **175**: 687–695.
- 93 Alexander H, Paller AS, Traidl-Hoffmann C *et al*. The role of bacterial skin infections in atopic dermatitis: expert statement and review from the international eczema council skin infection group. *Br J Dermatol* 2020; **182**: 1331–1342.
- 94 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: 33.e1–33.e8.
- 95 Schlievert PM, Case LC, Strandberg KL, Abrams BB, Leung DYM. Superantigen profile of Staphylococcus aureus isolates from patients with steroid-resistant atopic dermatitis. *Clin Infect Dis* 2008; **46**: 1562– 1567.
- 96 Wollenberg A, Zoch C, Wetzel S, Plewig G, Przybilla B. Predisposing factors and clinical features of eczema herpeticum: a retrospective analysis of 100 cases. J Am Acad Dermatol 2003; 49: 198–205.
- 97 Seegräber 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* 2020; 34: 1074–1079.
- 98 Ong PY, Leung DY. Bacterial and viral infections in atopic dermatitis: a comprehensive review. *Clin Rev Allergy Immunol* 2016; 51: 329–337.
- 99 Kreth HW, Hoeger PH. 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.
- 100 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: 1306–7.e2.
- 101 Osier E, Eichenfield L. The utility of Cantharidin for the treatment of Molluscum Contagiosum. *Pediatr Dermatol* 2015; 32: 295–296.
- 102 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.
- 103 Mathes EF, Oza V, Frieden IJ et al. "Eczema coxsackium" and unusual cutaneous findings in an enterovirus outbreak. *Pediatrics* 2013; 132: e149–e157.
- 104 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.
- 105 Lynch MD, Sears A, Cookson H et al. Disseminated coxsackievirus A6 affecting children with atopic dermatitis. *Clin Exp Dermatol* 2015; **40**: 525–528.
- 106 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.
- 107 Sparber F, De Gregorio C, Steckholzer S *et al.* The skin commensal yeast Malassezia triggers a type 17 response that coordinates anti-fungal immunity and exacerbates skin inflammation. *Cell Host Microbe* 2019; 25: 389–403.e6.
- 108 Thammahong A, Kiatsurayanon C, Edwards SW, Rerknimitr P, Chiewchengchol D. The clinical significance of fungi in atopic dermatitis. *Int J Dermatol* 2020; **59**: 926–935.

- 109 Glatz M, Bosshard PP, Hoetzenecker W, Schmid-Grendelmeier P. The role of Malassezia spp. in atopic dermatitis. J Clin Med 2015; 4: 1217– 1228.
- 110 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.
- 111 Kamata Y, Tominaga M, Takamori K. Itch in atopic dermatitis management. Curr Probl Dermatol 2016; 50: 86–93.
- 112 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.
- 113 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.
- 114 Silverberg JI, Yosipovitch G, Simpson EL *et al.* Dupilumab treatment results in early and sustained improvements in itch in adolescents and adults with moderate to severe atopic dermatitis: analysis of the randomized phase 3 studies SOLO 1 and SOLO 2, AD ADOL, and CHRONOS. *J Am Acad Dermatol* 2020; **82**: 1328–1336.
- 115 Agache I, Song Y, Posso M *et al*. Efficacy and safety of dupilumab for moderate-to-severe atopic dermatitis: a systematic review for the EAACI biologicals guidelines. *Allergy* 2021; **76**: 45–58.
- 116 Worm M, Simpson EL, Thaçi D *et al.* Efficacy and safety of multiple Dupilumab dose regimens after initial successful treatment in patients with atopic dermatitis: a randomized clinical trial. *JAMA Dermatol* 2020; **156**: 131–143.
- 117 Wollenberg A, Blauvelt A, Guttman-Yassky E *et al.* Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). *Br J Dermatol* 2021; **184**: 437– 449.
- 118 Simpson EL, Sinclair R, Forman S *et al*. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebocontrolled, phase 3 trial. *Lancet* 2020; **396**: 255–266.
- 119 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.
- 120 Guttman-Yassky E, Teixeira HD, Simpson EL et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (measure up 1 and measure up 2): results from two replicate double-blind, randomised controlled phase 3 trials. *Lancet* 2021; **397**: 2151–2168.
- 121 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.
- 122 Jaworek A, Szafraniec K, Jaworek M, Matusiak Ł, Wojas-Pelc A, Szepietowski JC. Itch relief in atopic dermatitis: comparison of narrowband ultraviolet B radiation and cyclosporine treatment. *Acta Derm Venereol* 2020; **100**: adv00291.
- 123 Doherty V, Sylvester DG, Kennedy CT, Harvey SG, Calthrop JG, Gibson JR. Treatment of itching in atopic eczema with antihistamines with a low sedative profile. *BMJ* 1989; **298**: 96.
- 124 Henz BM, Metzenauer P, O'Keefe E, Zuberbier T. Differential effects of new-generation H1-receptor antagonists in pruritic dermatoses. *Allergy* 1998; 53: 180–183.
- 125 Langeland T, Fagertun HE, Larsen S. Therapeutic effect of loratadine on pruritus in patients with atopic dermatitis. A multi-crossover-designed study. *Allergy* 1994; **49**: 22–26.
- 126 La Rosa M, Ranno C, Musarra I, Guglielmo F, Corrias A, Bellanti JA. Double-blind study of cetirizine in atopic eczema in children. *Ann Allergy* 1994; 73: 117–122.

- 127 Wahlgren CF, Hägermark O, Bergström R. The antipruritic effect of a sedative and a non-sedative antihistamine in atopic dermatitis. *Br J Dermatol* 1990; **122**: 545–551.
- 128 Munday J, Bloomfield R, Goldman M et al. Chlorpheniramine is no more effective than placebo in relieving the symptoms of childhood atopic dermatitis with a nocturnal itching and scratching component. *Dermatology* 2002; 205: 40–45.
- 129 Hannuksela M, Kalimo K, Lammintausta K et al. Dose ranging study: cetirizine in the treatment of atopic dermatitis in adults. Ann Allergy 1993; 70: 127–133.
- 130 Chunharas A, Wisuthsarewong W, Wananukul S, Viravan S. Therapeutic efficacy and safety of loratadine syrup in childhood atopic dermatitis treated with mometasone furoate 0.1 per cent cream. *J Med Assoc Thai* 2002; 85: 482–487.
- 131 Kawakami T, Kaminishi K, Soma Y, Kushimoto T, Mizoguchi M. Oral antihistamine therapy influences plasma tryptase levels in adult atopic dermatitis. *J Dermatol Sci* 2006; **43**: 127–134.
- 132 Matterne U, Böhmer 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.
- 133 Wollenberg A, Christen-Zäch S, Taieb A et al. ETFAD/EADV eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. J Eur Acad Dermatol Venereol 2020; 34: 2717–2744.
- 134 Church MK, Maurer M, Simons FE et al. Risk of first-generation H(1)antihistamines: a GA(2)LEN position paper. Allergy 2010; 65: 459–466.
- 135 Adam K, Oswald I. The hypnotic effects of an antihistamine: promethazine. Br J Clin Pharmacol 1986; 22: 715–717.
- 136 Vermeulen FM, Gerbens LAA, Schmitt J *et al.* The European TREatment of ATopic eczema (TREAT) registry taskforce survey: prescribing practices in Europe for phototherapy and systemic therapy in adult patients with moderate-to-severe atopic eczema. *Br J Dermatol* 2020; **183**: 1073– 1082.
- 137 Archier E, Devaux S, Castela E *et al.* Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. *J Eur Acad Dermatol Venereol* 2012; 26 (Suppl 3): 22–31.
- 138 Stern RS, Liebman EJ, Vakeva L. Oral psoralen and ultraviolet-a light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. PUVA follow-up study. J Natl Cancer Inst 1998; 90: 1278–1284.
- 139 Stern RS, Nichols KT, Vakeva LH. Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet a radiation (PUVA). The PUVA follow-up study. N Engl J Med 1997; 336: 1041– 1045.
- 140 Perez HC, Benavides X, Perez JS *et al.* Basic aspects of the pathogenesis and prevention of non-melanoma skin cancer in solid organ transplant recipients: a review. *Int J Dermatol* 2017; **56**: 370–378.
- 141 Paul CF, Ho VC, McGeown C *et al*. Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study. *J Invest Dermatol* 2003; **120**: 211–216.
- 142 Marcil I, Stern RS. Squamous-cell cancer of the skin in patients given PUVA and ciclosporin: nested cohort crossover study. *Lancet* 2001; 358: 1042–1045.
- 143 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.
- 144 Nankervis H, Pynn EV, Boyle RJ et al. House dust mite reduction and avoidance measures for treating eczema. Cochrane Database Syst Rev 2015; 1: Cd008426.
- 145 Fieten KB, Weststrate AC, van Zuuren EJ, Bruijnzeel-Koomen CA, Pasmans SG. Alpine climate treatment of atopic dermatitis: a systematic review. *Allergy* 2015; **70**: 12–25.
- 146 Thorsteinsdottir S, Thyssen JP, Stokholm J, Vissing NH, Waage J, Bisgaard H. Domestic dog exposure at birth reduces the incidence of atopic dermatitis. *Allergy* 2016; **71**: 1736–1744.

- 147 Pelucchi C, Galeone C, Bach JF, La Vecchia C, Chatenoud L. Pet exposure and risk of atopic dermatitis at the pediatric age: a meta-analysis of birth cohort studies. J Allergy Clin Immunol 2013; 132: 616–22.e7.
- 148 Kim A, Silverberg JI. A systematic review of vigorous physical activity in eczema. Br J Dermatol 2016; 174: 660–662.
- 149 Murota H, Yamaga K, Ono E, Katayama I. Sweat in the pathogenesis of atopic dermatitis. *Allergol Int* 2018; 67: 455–459.
- 150 Murota H, Yamaga K, Ono E, Murayama N, Yokozeki H, Katayama I. Why does sweat lead to the development of itch in atopic dermatitis? *Exp Dermatol* 2019; 28: 1416–1421.
- 151 Jaros J, Wilson C, Shi VY. Fabric selection in atopic dermatitis: an evidence-based review. Am J Clin Dermatol 2020; 2: 467–482.
- 152 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.
- 153 Bao Q, Chen L, Lu Z et al. Association between eczema and risk of depression: a systematic review and meta-analysis of 188,495 participants. J Affect Disord 2018; 238: 458–464.
- 154 Ronnstad ATM, Halling-Overgaard AS, Hamann CR, Skov L, Egeberg A, Thyssen JP. Association of atopic dermatitis with depression, anxiety, and suicidal ideation in children and adults: a systematic review and meta-analysis. J Am Acad Dermatol 2018; **79**: e30.
- 155 Chan CWH, Law BMH, Liu YH *et al.* The association between maternal stress and childhood eczema: a systematic review. *Int J Environ Res Public Health* 2018; **15**: 1–17.
- 156 Flanigan C, Sheikh A, DunnGalvin A, Brew BK, Almqvist C, Nwaru BI. Prenatal maternal psychosocial stress and offspring's asthma and allergic disease: a systematic review and meta-analysis. *Clin Exp Allergy* 2018; 48: 403–414.
- 157 Mochizuki H, Lavery MJ, Nattkemper LA *et al*. Impact of acute stress on itch sensation and scratching behaviour in patients with atopic dermatitis and healthy controls. *Br J Dermatol* 2019; **180**: 821–827.
- 158 Oh SH, Bae BG, Park CO et al. Association of stress with symptoms of atopic dermatitis. Acta Derm Venereol 2010; 90: 582–588.
- 159 Kantor R, Kim A, Thyssen JP, Silverberg JI. Association of atopic dermatitis with smoking: a systematic review and meta-analysis. J Am Acad Dermatol 2016; 75: 1119–1125.e1.
- 160 Pilz AC, Schielein MC, Schuster B *et al.* Atopic dermatitis: disease characteristics and comorbidities in smoking and non-smoking patients from the TREATgermany registry. *J Eur Acad Dermatol Venereol* 2022; 36: 413–421.
- 161 Tsakok T, Marrs T, Mohsin M *et al.* Does atopic dermatitis cause food allergy? A systematic review. *J Allergy Clin Immunol* 2016; **137**: 1071– 1078.
- 162 Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998; **101**: E8.
- 163 Sicherer SH, Sampson HA. Food hypersensitivity and atopic dermatitis: pathophysiology, epidemiology, diagnosis, and management. J Allergy Clin Immunol 1999; 104: S114–S122.
- 164 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.
- 165 Reekers R, Busche M, Wittmann M, Kapp A, Werfel T. Birch pollenrelated foods trigger atopic dermatitis in patients with specific cutaneous T-cell responses to birch pollen antigens. *J Allergy Clin Immunol* 1999; 104: 466–472.
- 166 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.

- 167 Isolauri E, Arvola T, Sütas Y, Moilanen E, Salminen S. Probiotics in the management of atopic eczema. *Clin Exp Allergy* 2000; **30**: 1604–1610.
- 168 Fölster-Holst R, Müller F, Schnopp N *et al.* Prospective, randomized controlled trial on lactobacillus rhamnosus in infants with moderate to severe atopic dermatitis. *Br J Dermatol* 2006; **155**: 1256–1261.
- 169 Rosenfeldt V, Benfeldt E, Nielsen SD *et al.* Effect of probiotic lactobacillus strains in children with atopic dermatitis. *J Allergy Clin Immunol* 2003; **111**: 389–395.
- 170 Grüber C. Probiotics and prebiotics in allergy prevention and treatment: future prospects. *Expert Rev Clin Immunol* 2012; **8**: 17–19.
- 171 Makrgeorgou A, Leonardi-Bee J, Bath-Hextall FJ et al. Probiotics for treating eczema. Cochrane Database Syst Rev 2018; 11: Cd006135.
- 172 Tan-Lim CSC, Esteban-Ipac NAR, JBV M 3rd *et al.* Comparative effectiveness of probiotic strains for the treatment of pediatric atopic dermatitis: a systematic review and network meta-analysis. *Pediatr Allergy Immunol* 2020; **32**: 124–136.
- 173 Bath-Hextall FJ, Jenkinson C, Humphreys R, Williams HC. Dietary supplements for established atopic eczema. *Cochrane Database Syst Rev* 2012: Cd005205.
- 174 Senra MS, Wollenberg A. Psychodermatological aspects of atopic dermatitis. Br J Dermatol 2014; 170(Suppl 1): 38–43.
- 175 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.
- 176 Stalder JF, Bernier C, Ball A *et al.* Therapeutic patient education in atopic dermatitis: worldwide experiences. *Pediatr Dermatol* 2013; **30**: 329–334.
- 177 de Bes J, Legierse CM, Prinsen CA, de Korte J. Patient education in chronic skin diseases: a systematic review. Acta Derm Venereol 2011; 91: 12–17.
- 178 Ersser SJ, Cowdell F, Latter S *et al.* Psychological and educational interventions for atopic eczema in children. *Cochrane Database Syst Rev* 2014; 2014: Cd004054.
- 179 Hamann CR, Egeberg A, Wollenberg A, Gislason G, Skov L, Thyssen JP. Pregnancy complications, treatment characteristics and birth outcomes in women with atopic dermatitis in Denmark. J Eur Acad Dermatol Venereol 2019; 33: 577–587.
- 180 Chi CC, Wang SH, Wojnarowska F, Kirtschig G, Davies E, Bennett C. Safety of topical corticosteroids in pregnancy. *Cochrane Database Syst Rev* 2015: Cd007346.
- 181 Agency EM. Neoral Soft Gelatin Capsules Summary of ProductCharacteristics (SmPC) – (emc).
- 182 Williams HC. Clinical practice. Atopic dermatitis. N Engl J Med 2005; 352: 2314–2324.
- 183 Rudikoff D, Cohen SR, Scheinfeld N. Clinical aspects and differential diagnosis of atopic dermatitis. In Rudikoff D, Cohen SR, Scheinfeld N, eds. Atopic Dermatitis and Eczematous Disorders. London: CRC Press, 2014.
- 184 Marrs T, Perkin MR, Logan K *et al.* Bathing frequency is associated with skin barrier dysfunction and atopic dermatitis at three months of age. J Allergy Clin Immunol Pract 2020; 8: 2820–2822.
- 185 Ruff SMD, Engebretsen KA, Zachariae C et al. The association between atopic dermatitis and hand eczema: a systematic review and metaanalysis. Br J Dermatol 2018; 178: 879–888.
- 186 Kaminski-Hartenthaler A, Meerpohl JJ, Gartlehner G et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. Z Evid Fortbild Qual Gesundhwes 2014; 108: 413–420.