EUROGUIDERM GUIDELINE ON ATOPIC ECZEMA

Version *2.1*, December 2022

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

Affiliations:

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

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

[3] Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Dermatology, Venereology and Allergology, Division of Evidence-Based Medicine (dEBM), Charitéplatz 1, 10117 Berlin, Germany

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

[5] Nantes Université, Department of Dermatology, CHU Nantes, UMR 1280 PhAN, INRAE, F-44000 Nantes, France

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

[7] Children'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, United Kingdom

[8] Dermatology Department, University of Brescia, Brescia, Italy

[9] University Hospital Lausanne, Lausanne, Switzerland

[10] Aarhus University Hospital, Aarhus, Denmark
[11] Global Allergy and Airways diseases Patient Platform GAAPP, Vienna, Austria
[12] Department of Dermatology, University Hospital Basel, Basel, Switzerland
[13] Dept. of Dermatology of the University of Debrecen, Debrecen, Hungary
[14] Department of Dermatology, Amsterdam UMC (University Medical Centers), Amsterdam, The Netherlands
[15] Dept. Dermatology, Univ. Giessen, Giessen, Germany
[16] Dermatology and Venereology Section, Department of Medicine, University of Verona, Verona, Italy
[17] Faculty of Medicine, National and Kapodistrian University of Athens, Athens, Greece
[18] Dept. of Dermatology and Allergy Centre, Odense University Hospital, University of Southern Denmark, Odense, Denmark
[19] Dept. of Dermato-Venerology, Aarhus University Hospital, Aarhus, Denmark
[20] Eczema Outreach Support (UK), Linlithgow, The United Kingdom
[21] Dermatology Department, Oslo University Hospital, Oslo, Norway
[22] Dept Dermatology Allergology Biederstein, Technical University Munich, Munich, Germany
[23] Dermatology Unit, Spedali Civili Hospital Brescia, Brescia, Italy
[24] Dermatology, Hospital of Sant Pau, Barcelona, Spain
[25] Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[26] Pediatric dermatology unit, Heim Pál National Children's Institute Budapest, Budapest, Hungary
[27] Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland
[28] Hospital Infantil Niño Jesús, Madrid, Spain
[29] Hannover Medical School, Hannover, Germany
[30] St John's Institute of Dermatology, King's College London, London, The United Kingdom
[31] Guy's & St Thomas' NHS Foundation Trust, London, The United Kingdom

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I. Notes on use/Disclaimer

The EuroGuiDerm Guideline on Atopic Eczema was developed in accordance with the EuroGuiDerm Methods Manual *v1.3*, which can be found on the website of the European Dermatology Forum (EDF) , subsection EuroGuiDerm/EDF Guidelines https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html.

II. Accompanying documents

- *Methods Report*
- *Evidence Report*
- *Implementation Slides*
- *Publications*

III. Funding (standard) Statement

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 raised funds in one account. The EuroGuiDerm Team is not involved in fundraising or in the decision making on which guideline (GL) or consensus statement (CS) development is funded. The decisions on which GL/CS is funded are made by the EuroGuiDerm Board of Directors independently. The EDF or any other body supporting the EuroGuiDerm is never involved in the guideline development and had no say on the content or focus of the guideline.

IV. Scoping and defining the purpose of the guideline

The aim of this guideline is to provide guidance on the management and treatment of patient with atopic eczema (AE) of all severities and age groups. According to the scoping document, the objectives of the guideline are:

- To generate recommendations and treatment algorithms on topical therapy, phototherapy as well as novel and established systemic treatments for AE, based on the latest evidence.
- Provide guidance in the management of AE patients during pregnancy and AE patients with allergic and other comorbidities.

V. Population and health questions covered by the guideline

The target population are patients with AE of all ages. Major health questions (regardless of sex, ethnicity or gender) regarding AE are:

- What is the optimal treatment with regard to patients' needs, taking efficacy, safety/tolerability of different treatment options and comorbidities into consideration?
- How should the selected treatment option best be managed and monitored?

Whenever possible and feasible, the recommendations are evidence-based, taking into account the results of systematic evidence synthesis based on rigorous methods as well as on the practical experience obtained by the expert group.

VI. Targeted users of this guideline

This guideline has been prepared for physicians, especially dermatologists, paediatricians, allergists, general practitioners and other specialists taking care of patients suffering from AE. Patients and care-givers may also be able to get reliable information and advice with regard to evidence-based therapeutic modalities.

VII. Treatment and treatment goals

Terminology	Definition
Acute flare	Clinically significant worsening of signs and symptoms of AE requiring therapeutic intervention.
Acute intervention	Treatments that address acute flares and typically lead to treatment response within days (in contrast to 'maintenance treatment').
Short term	When used in the context of clinical trials this refers to treatment up to 16 weeks.
Reactive	Treatment initiations or adaptations in response to a visible change in disease severity, in particular disease flares (in contrast to 'proactive' treatment).
Long term	When used in the context of clinical trials this refers to treatment longer than 16 weeks.
Proactive	Intermittent (typically twice a week) application of anti-inflammatory therapy to previously affected skin, in addition to an ongoing emollient treatment of unaffected and affected skin (in contrast to 'reactive' treatment)
Maintenance treatment	Regular, usually daily application of topical or systemic therapy for several months (in contrast to 'acute intervention').

Treatment goals

Treatment goal	Definition
Remission/Control	Satisfactory reduction of the signs and symptoms of AE whilst being on a safe long-term anti-inflammatory treatment.
Complete remission	Disappearance of the signs and symptoms of AE without use of anti-inflammatory treatment.

VIII. Methods Section

The EuroGuiDerm guideline on AE was developed in accordance with the EuroGuiDerm Methods Manual v1.3. For the detailed description of the guideline development process as well as an overview of the evidence referred to, please see the EuroGuiDerm guideline on AE Methods Report and the Evidence Report.

Both are available alongside the guideline document on the EDF website: https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html *(will became available after external review)*

Nomination of experts, management of conflicts of interest

The guideline development group comprised 26 experts from twelve countries nominated by EuroGuiDerm national partner societies or the two guideline co-coordinators (AW and CF). All nominations were reviewed and confirmed by the EuroGuiDerm Board of Directors. In addition, three patient representatives participated in the guideline development.

38% of the experts declared personal-financial interests (for details on classification see EuroGuiDerm Methods Manual v1.3.). *These members were neither eligible to take the lead in a respective working group nor for voting on recommendations pertaining to systemic treatment and on the stepped-care plan.*

Development of the guideline and the consensus process

The chapters of the guideline and the recommendations had been developed by the group members, who formed a number of working groups. Each chapter and all recommendations were reviewed, discussed and amended where appropriate by the entire group. All texts and recommendations were voted on with a necessary minimal agreement of >50% during the consensus conferences. AN facilitated all four consensus conferences using a structured consensus technique. Both internal and external review were conducted. Dissemination and implementation plans were developed. For more details, see Methods Report.

The wording of the recommendations was standardized (as suggested by the GRADE Working Group [1]).

Wording of recommendations

Strength	Wording	Symbols	Implications
Strong recommendation **for** the use of an intervention	'We recommend . . .'	↑↑	We believe that all or almost all informed people would make that choice.
Weak recommendation **for** the use of an intervention	'We suggest . . .'	↑	We believe that most informed people would make that choice, but a substantial number would not.
No recommendation with respect to an intervention	'We cannot make a recommendation with respect to . . .'	0	At the moment, a recommendation in favour or against an intervention cannot be made due to certain reasons (e.g. no reliable evidence data available, conflicting outcomes, etc.)

Weak recommendation **against** the use of an intervention	'We suggest against . . .'	↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
Strong recommendation **against** the use of an intervention	'We recommend against . . .'	↓↓	We believe that all or almost all informed people would make a choice against that intervention.

The recommendation are presented throughout this guideline as displayed below: alongside the wording of the recommendations the arrow(s) and colors indicate the direction and the strength of each recommendation. The rate of agreement (consensus strength) is also displayed as the actual percentage and in form of a category-type pie chart. For all systemic drugs, we added the dosages (according to the European Medical Agency). Additionally, the certainty of evidence was added where applicable (bold – significant difference; Associations are reported in line with Drucker et. al[2]).

We **suggest** using azathioprine in AE patients who are candidates for systemic treatment.	↑	>75%  (14/15) Evidence and consensus based, see Evidence Report

azathioprine: off licence; commonly used dosage
adults: 1-3 mg/kg per day
children: 1-3 mg/kg per day

Certainty of evidence[2, 3]:

Short term (8-16 weeks) vs placebo (NMA medications used in clinical practice or likely to be approved soon)

⊕⊕⊕○ MODERATE for standardized mean difference **change in signs**

⊕⊕○○ LOW for standardized mean difference QoL, itch

For azathioprine versus other drugs, see Evidence Report

Update 2022

The first update of the guideline was initiated to include abrocitinib in the guideline. Abrocitinib was approved by the EMA after the last consensus conference, which is why there was no recommendation for it in the old guideline. In addition, an update of the network meta-analysis by Drucker et al. has been published in March 2022.[2]

The new evidence from the updated network meta-analysis and new versions oft the stepped-care plans and drug tables were presented to the GDG in an online survey. All recommendations from the old version on systemic therapy were voted on again based on the new evidence. In addition, a new recommendation on abrocitinib and two modified recommendations from the old version on the sections on pregnancy and breastfeeding in which tralokinumab or abrocitinib were added were voted on. The updated stepped-care plans and the drug tables, in which abrocitinib was added were also re-

voted. All experts were asked to vote (agree / disagree/comment). Alternative suggestions could be entered as a reply option. Experts could not see how others had voted. Only the EuroGuiDerm Team had access to the results. All authors could participate but the votes of those with personal financial conflicts of interest did not count.

For the first update in 2022, the group comprised experts from twelve countries. Eleven experts (39.3%) declared personal-financial conflicts of interest, see below.

Title	First name	Last name	Personal- financial conflicts of interest
	Bernd	Arents	None
Dr.	Nora	Aszodi	None
Prof. Dr.	Sebastien	Barbarot	S Barbarot is an investigator or speaker for Almirall, Sanofi-Genzyme, Abbvie, Leo-Pharma, Pfizer, Eli Lilly
Prof. Dr.	Thomas	Bieber	T. Bieber was speaker and/or consultant and/or Investigator for AbbVie, Affibody, Almirall, AnaptysBio, Arena, Asana Biosciences, ASLAN pharma, Bayer Health, BioVerSys, Böhringer-Ingelheim, Bristol-Myers Squibb, Connect Pharma, Dermavant, DIECE Therapeutics, Domain Therapeutics, EQRx, Galderma, Glenmark, GSK, Incyte, Innovaderm, IQVIA, Janssen, Kirin, Kymab, LEO, LG Chem, Lilly, L´Oréal, MSD, Novartis, Numab, OM-Pharma, Pfizer, Pierre Fabre, Q32bio, RAPT, Sanofi/Regeneron, UCB. He is founder and chairman of the board of the non-profit biotech “Davos Biosciences”.
Dr.	Helen A.	Brough	None
Prof. Dr.	Piergiacomo	Calzavara Pinton	Speaker at congresses for LEO, Sanofi, Abbvie
Dr.	Stéphanie	Christen-Zäch	None
Dr.	Mette	Deleuran	Advisory board member, safety board member and/or speaker for the following companies: La Roche Posay, Pierre Fabre, Sanofi-Genzyme, Regeneron, Leo Pharma, ARENA Pharmaceuticals, ASLAN Pharmaceuticals, Kymab, Incyte, AbbVie, and Lilly
Prof. Dr.	Carsten	Flohr	None
Dr.	Nicole	Fosse	None
Dr.	Krisztián	Gáspár	None
Dr.	Louise	Gerbens	None
Prof. Dr.	Uwe	Gieler	None
Prof. Dr.	Giampiero	Girolomoni	Dr. Girolomoni has received personal fees from AbbVie, Almirall, Amgen, Biogen, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli-Lilly, Fresenius Kabi, Galderma, Genzyme, Leo Pharma, Novartis, Pfizer, Regeneron, Samsung bioepis, Sanofi and UCB.
Prof. Dr.	Stamatis	Gregoriou	None

Prof. Dr.	Charlotte	Mortz	None
MD PhD	Uffe	Nygaard	None
MD PhD	Eva Maria	Rehbinder	None
Prof. Dr. Dr.	Johannes	Ring	Honoraria as speaker or advisory board member: AbbVie, Allergika, ALK abello, Bencard, Galderma, Leo, Pfizer, Sanofi, viatris
Dr.	Mariateresa	Rossi	None
	Christine	Roxburgh	None
Dr.	Esther	Serra-Baldrich	None
Prof. Dr.	Dagmar	Simon	None
Prof. Dr.	Zsuzsanna	Szalai	Sanofi, AbbVie
Prof. Dr.	Jacek C.	Szepietowski	Advisory Board member/Consultant - Sanofi-Genzyme, Pfizer Speaker - Abbvie, Sanofi-Genzyme, Pfizer Investigator - Regeneron, Abbvie, Pfizer
Dr.	Antonio	Torrelo	Investigator for Lilly, Galderma, Pfizer Advisor and/or lecturer for Lilly, Sanofi, Pfizer, Novartis, Pierre Fabre
Prof. Dr.	Thomas	Werfel	TW has received institutional grants or personal fees for lectures or advisory boards from AbbVie, Almirall, Eli Lilly, Galderma, Janssen/JNJ, Leo Pharma, Novartis, Pfizer, Regeneron/Sanofi.
Prof. Dr. med. Dr. h.c.	Andreas	Wollenberg	I have received honoraria for attending advisory boards from pharmaceutical companies producing biologics and small molecules and topical drugs for treatment of atopic dermatitis (e.g. Abbvie, Aileens, Almirall, Amgen, BMS, Galapagos, Galderma, GSK, Janssen, Leo Pharma, Eli Lilly, MedImmune, Merck, Novartis, Pfizer, Pierre Fabre, Regeneron, Sanofi-Aventis).

Evidence

The living systematic review by Drucker and colleagues[3] was used as the evidence base based on which we created an evidence-to-decision framework (see Evidence Report). Furthermore, challenges exist with comparing clinical trials in AE due to their differences in trial design, including study comparators, rules for rescue treatment, washout periods for topical and systemic treatments, inclusion criteria, and the duration of the screening period.[4] Finally, this analysis does not take into consideration the overall management plan that targets long-term stabilization, flare prevention and avoidance of side-effects beyond 16 weeks[5]. We only summarize the results here. For limitations please refer to the website.

For each recommendations that is evidence-based, we added the certainty of the evidence when compared to placebo[2]. The assessment of the certainty of evidence leads to four grades, see Figure 1 (Table 5.1. GRADE Handbook[6]).

High ⊕⊕⊕⊕: we are **very confident** that the true effect lies close to that of the estimate of the effect.
Medium ⊕⊕⊕◯: we are **moderately confident** in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⊕⊕◯◯: our **confidence in the effect estimate is limited: The true effect may be substantially different** from the estimate of the effect.
Very low ⊕◯◯◯: we have **very little confidence** in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Figure 1 Definitions of "certainty of evidence" [6]

Excerpt from the publication of the network meta-analysis 'Systemic Immunomodulatory Treatments for Atopic Dermatitis - Update of a Living Systematic Review and Network Meta-analysis' by Aaron M. Drucker and colleagues, March 2022.[2]

„[…] Up to 16 weeks of treatment in adults, abrocitinib, 200 mg daily (MD, 2.2; 95% CrI, 0.2-4.0; high certainty) and upadacitinib, 30 mg daily (MD, 2.7; 95% CrI, 0.6-4.7; high certainty) were associated with reduced EASI scores slightly more than dupilumab, 600 mg then 300 mg every 2 weeks. Abrocitinib, 100 mg daily (MD, −2.1; 95% CrI, −4.1 to −0.3; high certainty), baricitinib, 4 mg daily (MD, −3.2; 95% CrI, −5.7 to −0.8; high certainty), baricitinib, 2 mg daily (MD, −5.2; 95% CrI, −7.5 to −2.9; high certainty), and tralokinumab, 600 mg then 300 mg every 2 weeks (MD, −3.5; 95% CrI, −5.8 to −1.3; high certainty) reduced EASI slightly less than dupilumab and there was little or no difference between upadacitinib, 15 mg daily, and dupilumab (MD, 0.2; 95% CrI, −1.9 to 2.2; high certainty). The pattern of results was similar for change in POEM […], DLQI […], and PP-NRS […].

In SMD analyses, the relative outcomes of conventional systemic agents vs dupilumab were similar to our baseline network meta-analyses […]. Higher-dose cyclosporine was associated with improved clinical signs slightly better than dupilumab (SMD, −0.2; 95% CrI, −0.8 to 0.5; low certainty). Lower-dose cyclosporine (SMD, 0.2; 95% CrI, −0.5 to 0.8; low certainty), methotrexate (SMD, 0.2; 95% CrI, −0.4 to 0.9; low certainty), and azathioprine (SMD, 0.3; 95% CrI, −0.1 to 0.7; low certainty) were associated with reduced signs slightly less than dupilumab, but certainty of evidence was low owing to concerns related to risk of bias of included trials and imprecision reflected in wide credible intervals.

[…] For withdrawal owing to adverse events among patients receiving abrocitinib, baricitinib, dupilumab, tralokinumab, upadacitinib, and placebo, credible intervals were wide, contributing to lower certainty evidence, so we were unable to make clinically useful conclusions […]. Abrocitinib, 100 mg daily, was associated with more serious adverse events than dupilumab (OR, 2.6; 95% CrI, 1.1-6.4; low certainty) and dupilumab was associated with fewer serious adverse events than placebo (OR, 0.5; 95% CrI, 0.3-0.8;moderate certainty)" page 526 and 527, Drucker et al. 2022[2]

Linking evidence to recommendations

In the table below, we link the evidence from the NMA directly to the recommendations made. For additional information and justifications, please see the corresponding chapters.

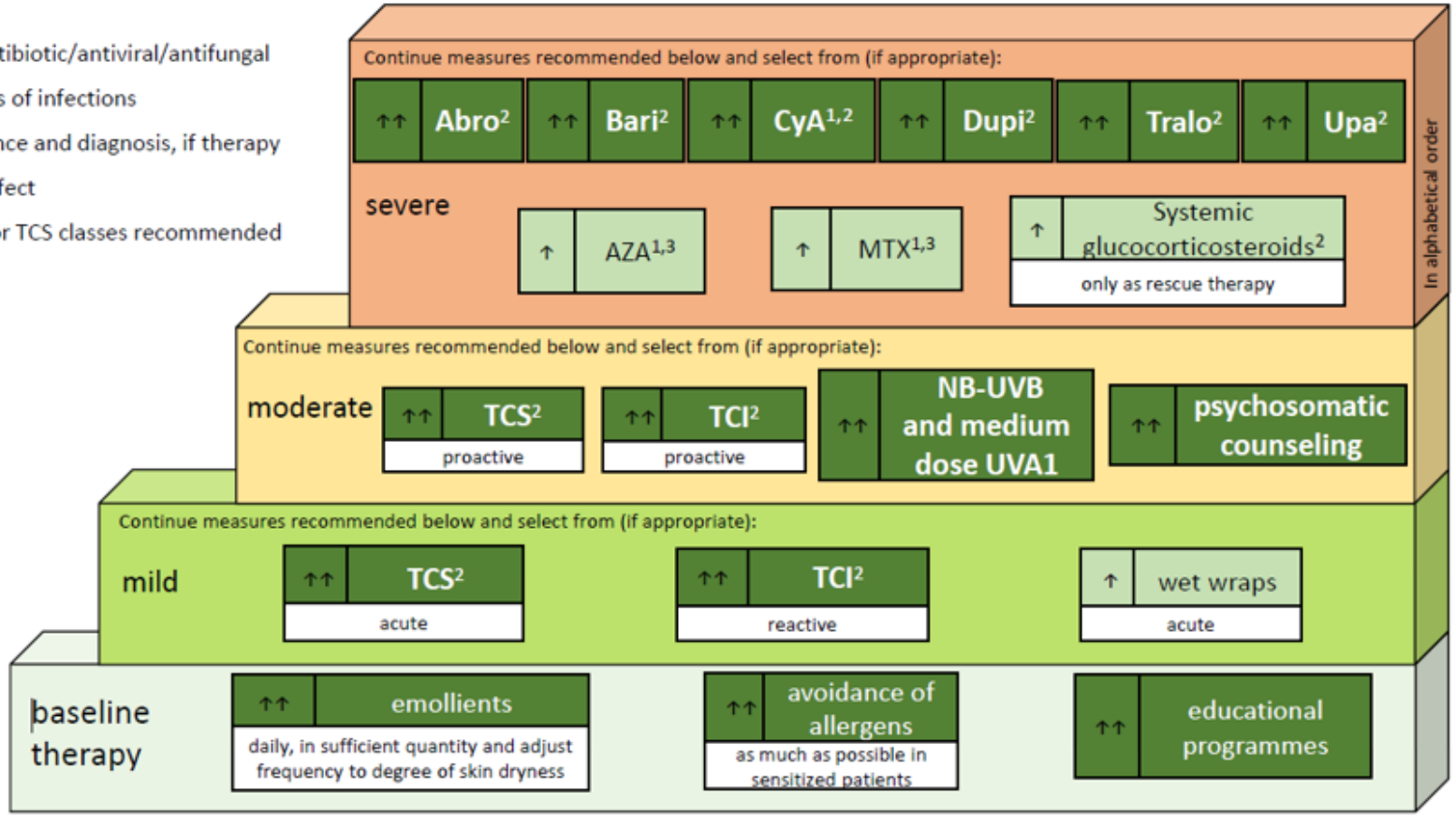
Recommendation	**Short term (8-16 weeks) vs placebo** Bold = statistically significant difference
We suggest using azathioprine in AE patients who are candidates for systemic treatment.	⊕⊕⊕◯ MODERATE for standardized mean difference **change in signs** ⊕⊕◯◯ LOW for standardized mean difference QoL, itch
We recommend using ciclosporin to achieve disease control in AE patients who are candidates for systemic treatment.	⊕⊕⊕◯ MODERATE for standardized mean difference **change in signs** ⊕⊕⊕◯ MODERATE - ⊕⊕◯◯ LOW for standardized mean difference QoL ⊕⊕◯◯ LOW for standardized mean difference itch
We suggest using methotrexate in AE patients who are candidates for systemic treatment.	⊕⊕◯◯ LOW for standardized mean difference change in signs, Qol, itch
We recommend dupilumab in AE patients who are candidates for systemic treatment.	⊕⊕⊕⊕ HIGH for mean difference/ standardized mean difference **EASI, change in signs, POEM, peak pruritus NRS, DLQI, QoL, itch** ⊕⊕⊕◯ MODERATE - ⊕⊕◯◯ LOW for undesirable effects
We recommend tralokinumab in AE patients, who are candidates for systemic treatment.	⊕⊕⊕⊕ HIGH for mean difference/ standardized mean difference **EASI, change in signs, POEM, peak pruritus NRS, DLQI, QoL, itch** ⊕⊕◯◯ LOW for undesirable effects
We recommend abrocitinib in AE patients who are candidates for systemic treatment.	⊕⊕⊕⊕ HIGH for mean difference/ standardized mean difference **EASI, change in signs, POEM, peak pruritus NRS, DLQI, QoL, itch** ⊕⊕◯◯ LOW - ⊕◯◯◯ VERY LOW for undesirable effects
We recommend baricitinib in AE patients who are candidates for systemic treatment.	⊕⊕⊕⊕ HIGH for mean difference/ standardized mean difference **EASI, change in signs, POEM, peak pruritus NRS, DLQI, QoL, itch** ⊕⊕◯◯ LOW - ⊕◯◯◯ VERY LOW for undesirable effects
We recommend upadacitinib in AE patients who are candidates for systemic treatment	⊕⊕⊕⊕ HIGH for mean difference/ standardized mean difference **EASI, change in signs, POEM, peak pruritus NRS, itch** ⊕⊕⊕◯ MODERATE - ⊕⊕◯◯ LOW for undesirable effects

AE = atopic eczema; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; NMA = network meta analysis; OR = Odds ratio; POEM = Patient-Oriented Eczema Measure; PPNRS = Peak Pruritus Numerical Rating Scale; RoB = Risk of Bias; VAS = visual analog scale

IX. Recommendations

EuroGuiDerm Guideline on Atopic Eczema
Stepped-care plan for adults with atopic eczema

- Add antiseptic/antibiotic/antiviral/antifungal treatment in cases of infections
- Consider compliance and diagnosis, if therapy has insufficient effect
- Refer to table 3 for TCS classes recommended

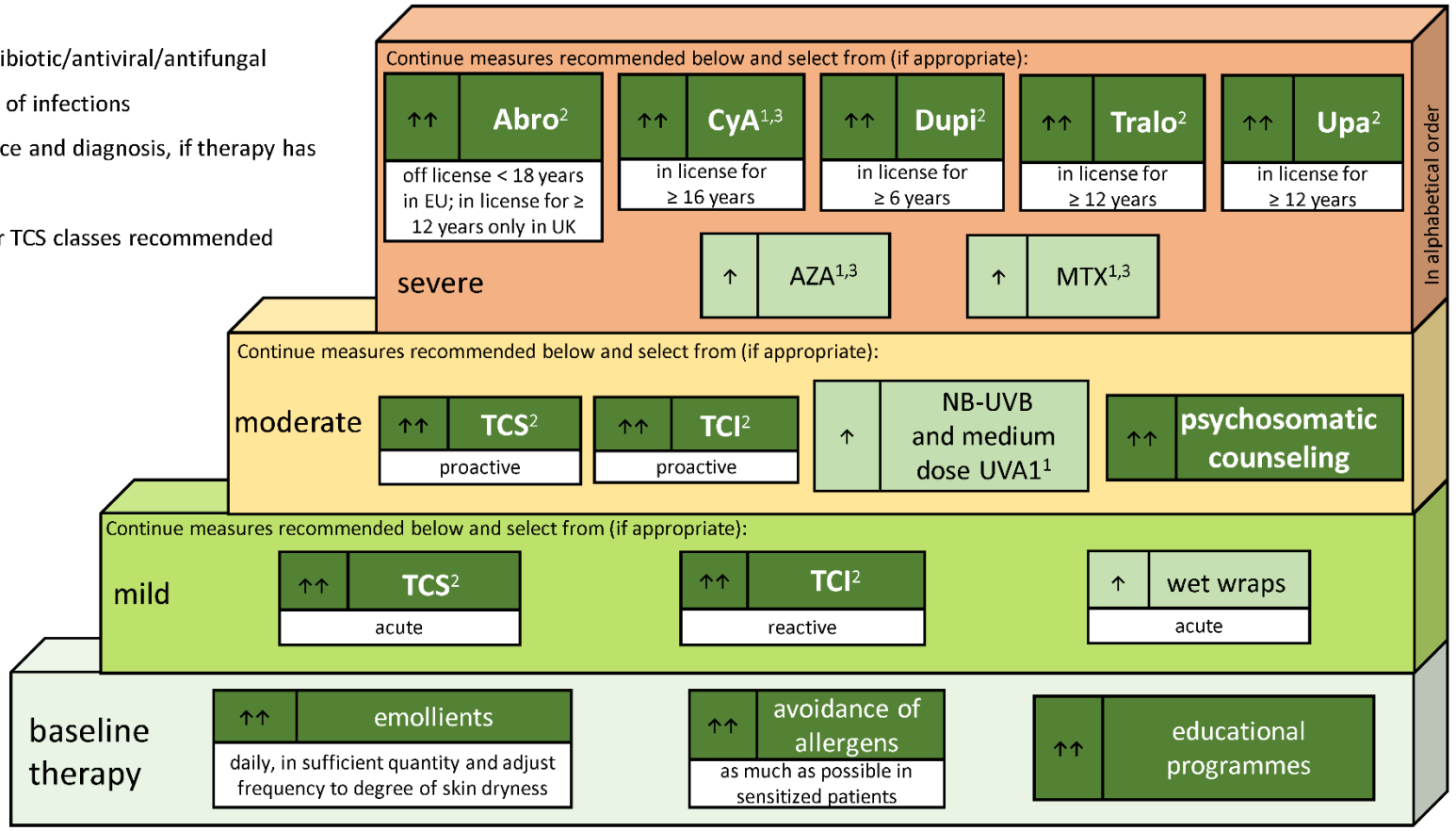


[1] refer to guideline text for restrictions, [2] licensed indication, [3] off-label treatment
↑↑ (dark green) strong recommendation for the use of an intervention / ↑ (light green) weak recommendation for the use of an intervention
For definitions of disease severity, acute, reactive, proactive see section 'VII' and section 'Introduction to systemic treatment' of the EuroGuiDerm Atopic Eczema Guideline
Abro= abrocitinib; AZA=azathioprine; Bari=baricitinib; CyA=ciclosporin; Dupi=dupilumab; MTX=methotrexate; TCI=topical calcineurin inhibitors; TCS= topical corticosteroids; Tralo=tralokinumab; Upa=upadacitinib; UVA1=ultraviolet A1; NB-UVB=narrow-band ultraviolet B


>75%
13/15

EuroGuiDerm Guideline on Atopic Eczema
Stepped-care plan for children and adolescents with atopic eczema

- Add antiseptic/antibiotic/antiviral/antifungal treatment in cases of infections
- Consider compliance and diagnosis, if therapy has insufficient effect
- Refer to table 3 for TCS classes recommended



>75%
12/15

[1] refer to guideline text for restrictions, [2] licensed indication, [3] off-label treatment
↑↑ (dark green) strong recommendation for the use of an intervention / ↑ (light green) weak recommendation for the use of an intervention
For definitions of disease severity, acute, reactive, proactive see section 'VII' and section 'Introduction to systemic treatment' of the EuroGuiDerm Atopic Eczema Guideline
AZA=azathioprine; CyA=ciclosporin; Dupi=dupilumab; MTX=methotrexate; TCI=topical calcineurin inhibitors; TCS= topical corticosteroids; Upa=upadacitinib; UVA1=ultraviolet A1; NB-UVB=narrow-band ultraviolet B

Symbols	Implications (adapted from GRADE [1])
↑↑	We believe that all or almost all informed people would make that choice.
↑	We believe that most informed people would make that choice, but a substantial number would not.
0	We cannot make a recommendation.
↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
↓↓	We believe that all or almost all informed people would make a choice against that choice.
	No recommendation

Table 1: General recommendations for systemic drugs for AE adult patients, who are candidates for systemic treatment (for details see corresponding chapter)

	Conventional systemic treatments			Biologics		JAK-inhibitors			Rescue therapy
	Ciclosporin	**Methotrexate**	**Azathioprine**	**Dupilumab**	**Tralokinumab**	**Abrocitinib**	**Baricitinib**	**Upadacitinib**	**Systemic corticosteroids**
Recommendation	↑↑	↑	↑	↑↑	↑↑	↑↑	↑↑	↑↑	↑
Dose for adults[1]	licensed ≥ 16 years; standard dosage adults: 2.5-5 mg/kg per day in two single doses	off-label; commonly used dosage adults: initial dose: 5-15 mg/ per week; maximum dose: 25 mg/ week	off-label; commonly used dosage adults: 1-3 mg/kg per day	licensed ≥ 6 years; adults: initially 600 mg s.c. day 1 followed by 300 mg Q2W	licensed for adults; initially 600 mg s.c. day 1 followed by 300 mg Q2W; consider Q4W dosing at week 16 in those achieving clear or almost clear skin	licensed for adults; dosage adults: 200 mg per day, reduction to 100 mg per day possible, depending on treatment response; age ≥ 65: 100 mg per day; the lowest effective dose for maintenance should be considered	licensed for adults; dosage adults: 4 mg per day, reduction to 2 mg per day possible, depending on treatment response	licensed ≥ 12 years; dosage adults: 15 or 30 mg per day based on individual patient presentation; age ≥ 65: 15 mg per day; the lowest effective dose for maintenance should be considered	general unspecific licence for adults and children for steroid responsive skin disease; dosage maximum: 1 mg/kg per day
Time to response (weeks)[2]	1-2	8-12	8-12	4-6	4-8	1-2	1-2	1-2	1-2
Time to relapse (weeks, based on expert experience)[2]	<2	>12	>12	>8	> 8	<2	<2	<2	<2
Monitoring	complete blood count, renal and liver profile, blood pressure,	complete blood count, renal and liver profile, PIIINP if available, screen for chronic infections	complete blood count, renal and liver profile, TPMT activity if available, screen for chronic infections	not required	not required	complete blood count, lipid profile, liver profile	complete blood count, lipid profile, liver profile	complete blood count, lipid profile, liver profile	not required for short-term treatment, consider blood glucose and testing for adrenal gland suppression with high doses/longer-term treatment

Selection of most relevant adverse events	serum creatinine↑, blood pressure ↑	nausea, fatigue, liver enzymes ↑, myelotoxicity	gastrointestinal disturbances, idiosyncratic hypersensitivity reactions, hepatotoxicity, myelotoxicity	Conjunctivitis, upper respiratory tract infections, arthralgia	upper respiratory tract infections; conjunctitivitis	upper respiratory tract infections,, increase in LDL cholesterol; thrombocytopenia, increased creatine phosphokinase, nausea and abdominal pain herpes virus infections, acne	upper respiratory tract infections,, increase in LDL cholesterol; thrombocytosis, nausea and abdominal pain herpes virus infections, acne	upper respiratory tract infections, acne; headache, anaemia and neutropenia, CK elevation, increase in LDL cholesterol, nausea and abdominal pain herpes virus infections	skin atrophy, weight gain, sleep disturbance, mood changes, hyperglycaemia or new onset diabetes, peptic ulcers/gastritis, osteoporosis

[1] SmPC, [2]expert experience, ↑ rise, AE- atopic eczema; GL – guideline, LDL – low density lipoprotein, PIIINP - Procollagen III N-Terminal Propeptide, TPMT – Thiopurine-S-Methyltransferase

Symbols	Implications (adapted from GRADE [1])
↑↑	We believe that all or almost all informed people would make that choice.
↑	We believe that most informed people would make that choice, but a substantial number would not.
0	We cannot make a recommendation.
↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
↓↓	We believe that all or almost all informed people would make a choice against that choice.
	No recommendation.

Table 2: General recommendations for systemic drugs for special AE patient populations (for details see corresponding chapter)

	Conventional systemic treatments			Biologics		JAK inhibitors			Rescue therapy
	Ciclosporin	Methotrexate	Azathioprine	Dupilumab	Tralokinumab	Abrocitinib	Baricitinib	Upadacitinib	Systemic corticosteroids
Children and adolescents with AE who are candidates for systemic treatment	↑↑	↑	↑	↑↑	↑↑	↑↑		↑↑	
Dose for children	licensed for ≥ 16 years commonly used dosage children: 2.5-5 mg/kg per day in two single doses	off-label; 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	licensed for ≥ 12 years; initially 600 mg s.c. day 1 followed by 300 mg Q2W; consider Q4W dosing at week 16 in those achieving clear or almost clear skin	off-label; only in UK approved ≥ 12 years; commonly used dosage children: 100 mg per day	off-label	licensed for ≥ 12 years; age 12-17 (>= 30 kg bw): 15 mg per day	general unspecific licence for children for steroid responsive skin disease;; dosage maximum: 1 mg/kg per day
Pregnancy (in candidates for systemic treatment)	↑	↓↓	↑	0	0	↓↓	↓↓	↓↓	↑ prednisolone (0.5mg/kg/d) *only* as rescue therapy for acute flares
Breastfeeding	↓	↓	↓	0	0	↓	↓	↓	↑ prednisolone (0.5mg/kg/d) *only* as rescue therapy for acute flares

[1] SmPC; Q2W - once every 2 weeks

Symbols	Implications (adapted from GRADE [1])
↑↑	We believe that all or almost all informed people would make that choice.
↑	We believe that most informed people would make that choice, but a substantial number would not.
0	We cannot make a recommendation.
↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
↓↓	We believe that all or almost all informed people would make a choice against that choice.
	No recommendation.

Table 3: General recommendations for topical drugs for treatment of atopic eczema (for details see corresponding chapter)

Overall recommendation	TCS ↑↑		TCI ↑↑	
	TCS class I and II	TCS class III and IV	Tacrolimus 0.1% Tacrolimus 0.03%	Pimecrolimus 1%
For further information see background text	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 proactive treatment		in label for proactive treatment	not suitable for proactive treatment
Special considerations				
Suitable for **children > 2 to < 16** years of age	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 **pregnancy**	yes	yes	yes (0.03% & 0.1%)[1]	yes[1]
Suitable during **breastfeeding**	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 use

Symbols	Implications (adapted from GRADE [1])
↑↑	We believe that all or almost all informed people would make that choice.
↑	We believe that most informed people would make that choice, but a substantial number would not.
0	We cannot make a recommendation.
↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
↓↓	We believe that all or almost all informed people would make a choice against that choice.
	No recommendation.

X. Guideline text and recommendations

1. Patient's 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%  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%  Patient/caregiver consensus
We **recommend** that patients with co-morbidities are treated by multi-disciplinary teams.	↑↑	100%  Patient/caregiver consensus
We **recommend** that health care providers are given time, training and resources to educate patients/caregivers in lay language about treating and managing their own condition.	↑↑	100%  Patient/caregiver consensus
We **recommend** that patients/caregivers receive adequate knowledge, skills, resources and support to treat their AE at home and cope with its impact on life.	↑↑	100%  Patient/caregiver consensus

We **recommend** that patients have access to all available treatments and that these treatments are affordable and practical.	↑↑	100%  Patient/caregiver consensus

Burden of disease

The burden of disease in atopic eczema does not consist of symptoms only, but it affects life in general, for patients/caregivers, partner, family, etc. As a well as being a painful and frustrating condition, atopic eczema affects all aspects of life, from sleep to relationships, work/school and social activities. The condition can also negatively impact on self-esteem and psychological well-being, which may lead to anxiety and depression. Therefore the whole burden of the disease needs to be taken into account when treating patients with mild to severe atopic eczema, without any judgement on their personal experiences of the disease.[7]

Shared decision-making

Shared decisions about treatment choices between patient and clinician increase adherence to treatment and thus the patient's long term health outcomes. When the relationship is based on trust and understanding of the patient's deep beliefs in regards to their condition and their treatment options, compliance is further increased. This complies with the definition of Evidence Based Medicine as per Sackett *et al*.[8]

Multidisciplinary approach

Atopic and non-atopic co-morbidities are common. These include food allergies, allergic rhino-conjunctivitis and asthma, but also psychological and psychiatric diseases, such as anxiety and depression, which can profoundly affect the patient's physical, emotional and social life. In addition, the impact of atopic eczema on the patient's psychological well-being can be profound and require specialist intervention. Whilst in most cases atopic eczema can be treated by a general/family physician, dermatologist or paediatrician, in some cases a pulmonologist, allergist, ENT-specialist, ophthalmologist, specialised nurse, psychologist or social worker may be needed. The advantages of a multidisciplinary approach are a combined agreed treatment plan with no contradictory advice and better control of all aspects of atopic eczema and its co-morbidities. The severity of the skin condition, treatment adherence, sleep and overall quality of life will likely improve as a result.[9]

Adequate resources to educate patients

Basic treatment of atopic eczema includes the regular use of a range of topical treatments, as well as using strategies such as managing triggers. Due to the individual and complex nature of the condition, health care providers need adequate resources to teach patients/caregivers in lay language indispensable self-management skills. They also often need to address common concerns about topical corticosteroids, to avoid adherence problems.[10] In practice, however, many health care providers lack those resources, mostly due to lack of time, materials and standardised programmes.

Self-management of atopic eczema

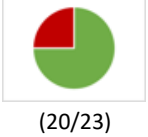
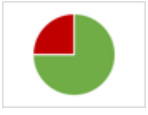
As already pointed out, the treatment of atopic eczema can be laborious, complex and confusing; to self-manage their atopic eczema successful, patients/caregivers require personalised education, guidance and on-going support by health care providers and patient networks. As atopic eczema can be a life-long disease, with serious exacerbations from time-to-time, it is important that patients/caregivers have timely access to these educational and support resources. Indeed, in many cases, escalation to more aggressive therapies or referrals to specialist care could be prevented by better self-management skills and adherence to treatment at home.[11]

Access to affordable and practical treatment

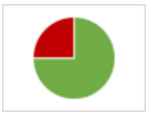
Many long-standing atopic eczema treatments such as emollients, topical corticosteroids, bandages and systemic therapy are generally accessible to patients; however, other treatments such as phototherapy, whilst also an option, may not be practical due to their burden on life (many hospital visits). New emerging systemic therapies offer much hope to patients with severe atopic eczema however they are not always available. Cost effective treatments should be made available and practical to all patients who would benefit from them.

For patients/caregivers, the cost of treating and managing atopic eczema includes purchasing treatments when these are not reimbursed (e.g. emollients in some countries), extra expenses to avoid triggers (special cosmetics, clothing, bedding, diets, etc.) and indirect costs for loss of education/income.[12] National healthcare provisions and insurance regulations vary widely country by country and for individuals, leading to significant health inequalities, which must be addressed urgently.

2. Basic emollients and moisturizers

We **recommend** gentle cleansing and bathing procedures especially in acutely inflamed or superinfected skin in patients with AE.	↑↑	100%  (18/18) Expert Consensus
We **suggest** bathing in moderately warm water over a short duration of time in patients with AE.	↑	>75%  (17/19) Expert Consensus
We **suggest against** the use of alkaline soaps in patients with AE.	↓	100%  (19/19) Expert Consensus
We **suggest** that patients with AE use body care products, for example gentle cleansers that do not contain potent irritants or relevant allergens.	↑	
We **recommend** daily use of emollients, liberally and frequently for patients with AE, as basic treatment of the disturbed skin barrier function.	↑↑	>75%  (20/23) Expert Consensus
We **suggest** using moisturizers with a hydrophilic formula in the summer and moisturizers with a higher lipid content in the winter in patients with AE.	↑	>75%  (15/18)[1] Expert Consensus

[1]1 Abstention

We **recommend** to apply emollients immediately after bathing or showering and soft pat drying ("soak and seal technique").	↑↑	100%  (19/19) Expert Consensus
We **recommend** the use of emollients as background treatment to prevent flares and to reduce the symptoms of AE.	↑↑	>75%  (18/19)[1] Expert Consensus

[1]1 Abstention

A disturbance of epidermal skin barrier function, clinically manifesting as dry skin, is one of the characteristic features of AE; there is evidence from animal experimental and human studies that the skin barrier anomaly is genetically driven and facilitates the penetration of allergens and other possible noxious substances into the upper skin at the same time leading to increased transepidermal water loss (TEWL).[13, 14]

Filaggrin mutation is the best known anomaly,[15] but alterations in proteases and protease inhibitors as well as alterated composition of intraepidermal epidermal lipids (cholesterol, ceramides, free fatty acids) are supposed to also play a role in the pathophysiology of this condition.[16-19] All procedures to improve disturbed skin barrier function or maintain normal function are often called 'skin care'; they also include measures to avoid irritant influences. It would be better to talk about 'basic therapy of disturbed skin barrier function' instead of 'skin care'. For emollient treatment often the term 'drug free vehicles' is used in order to distinguish this from pharmacotherapeutic modalities;[14, 20, 21] indeed only few emollients are registered as drugs but more often as cosmetics or medicinal products.[22-25]

The major principle of this basic therapy of disturbed skin barrier function is the introduction of lipids into the upper epidermis in order to restore the skin barrier.

2.1. Emollient therapy

Basic emollient therapy

Basic emollient therapy is the essence of every treatment of AE. [26, 27] 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 softened the delineation of pure emollients working through their physical properties from 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 vehicle-type substances plus additional active, non-medicated substances'*.[28]

A Cochrane review compared moisturizer containing emollients versus no moisturizer and found a better effect in reducing investigator reported severity as well as leading to fewer flares and reduced use of corticosteroids.[29] There were studies using glycerol-containing moisturizers versus vehicle or placebo.[23, 26] More participants in the glycerol group noticed skin improvement but the MID (minimal important difference) was not met.[30]

Some studies investigated oil-containing moisturizer 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 moisturizers was more effective than emollient treatment alone with various outcomes measured.[29, 31]

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.[32]

Only emollient preparation devoid of proteinaceous allergens or haptens known to cause contact allergy (such as lanolin/wool wax alcohol or preservatives such as methylisothiazolinone)[33] 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.[31, 34, 35]

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 basecontaining for instance 5 % urea or glycerol.[21]

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

According to the acuity of the skin condition, also lipophilic bases may be helpful, especially in more chronic conditions. The use of barrier ointments, bath oils, shower gels, emulsions or micellar solutions enhancing the barrier effect is also recommended.

The applied amount of the topical is crucial, about 250g/week are recommended.[36, 37] It may follow the finger-tip unit rule: a finger-tip unit (FTU) is the amount of ointment expressed from a tube with a 5 mm diameter nozzle and measured from the distal skin crease to the tip of the index finger (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.[20]

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).[38]

The use of pure oil products such as coconut or olive oil instead of emulsions will dry out the skin and increase the transepidermal water loss and thus is not recommended.[39]

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

Several non-medicated products for topical treatment of AE contain putative active ingredients, but are neither fulfilling the definition of nor needing a licence as a topical drug. These products, referred to as 'emollients plus' by the European guideline since 2018, may contain, for example, flavonoids such as licochalcone A, saponins and riboflavins from protein-free oat plantlet extracts[34], bacterial lysates from Aquaphilus dolomiae or Vitreoscilla filiformis species[40-42], or a synthetic derivative of menthol such as menthoxypropanediol.[28]

The oral supplementation with unsaturated fatty acids like gammalinolenic acid from evening primrose oil or eicosapentaenoic acid from fish oils have been studied as ingredients both improving barrier function as well as enhancing patient acceptance, showing conflicting results. [43, 44] The efficacy of topical evening primerose oil-containing emollients is dependend on the choice of vehicle.

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 like moisturizers or tannin, ammonium bituminosulfonate, flavonoids or unsaturated fatty acids like omega-3 or omega-6 compounds.

Prevention aspect

Use of emollients has 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 for atopy/AE, who were treated daily with emollients developed less atopic dermatitis and/or allergic sensitisations in the first year of life.[45, 46] Two larger and longer randomized controlled trials with a less stringent intervention did not confirm these effects.[47, 48] Some experienced clinicians still feel comfortable using emollients in individuals at risk for AE early in life.

Safety

The use of emollients is safe, except for occasional cases of contact allergy. Using emollients may be associated with irritative and allergic side effects. In patients for whom topical anti-inflammatory treatment is indicated, the use of emollients alone involves a considerable risk of disseminating bacterial or viral infections typical for AE.[49]

Emollients may contain ingredients eliciting contact sensitisation such as emulsifiers, preservatives or fragrances.[33, 50, 51] Depending upon the body site also local irritation such stinging or burning sensations may occur in individuals with "sensitive skin".[52] There is a high inter-individual variability in skin tolerability of topical preparations, which has to be considered in the management of AE patients.

Urea may cause irritation in infants and should be avoided in this age group, while toddlers should be treated with lower concentrations than adults. Glycerol seems to be better tolerated than urea plus sodium chloride.[26]

Propylene glycol is easily irritating in young children under two years of age.

Bath oils should not contain strong protein allergens. Peanut or coconut oil preparations may increase the risk of developing skin sensitisation. However, in refined products no protein allergens are present.[53]

2.2. Cleansing and bathing

Skin hygiene procedures play an important role in the management of AE, especially in infants and small children. Some authors consider alkaline soaps as disadvantageous compared to liquid cleansers with adequate skin surface pH and lipid content.[54] Bathing is regarded generally superior to washing or showering – especially in young children - also with regard to emotional and psychological interactions between infants and parents.[55, 56] The water temperature should also not be too high.[57] A recent systematic review has shown that daily bathing or showering is not associated with changes in disease severity, but 3 studies with qualitative analysis found an improvement of itch and IGA by bathing. Showering may be permitted.[58]

The skin must be cleansed thoroughly, but gently and carefully, in order 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, mechanical cleansing is probably more important. Cleansing agents are available in various galenic forms (syndets, aqueous solutions) and should not be too irritant and should not contain strong allergens.[33, 59] The pH values should be between 5 – 6. A small randomized study regarding the frequency of bathing procedures did not show any difference between twice weekly versus every day.[60]

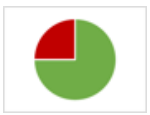
In infants, it is easier to perform the first stage of gentle cleansing on the nappy mattress rather than directly in the bathtub. The mechanical component of cleaning helps removing bacteria from the stratum corneum. A further cleansing is followed by a rapid rinse performed in the bath (27 – 30 °C). The short duration of the bath (ca. 5 minutes) and the use of bath oils (added for the last 2 minutes of bathing) are aimed at avoiding epidermal dehydration. Topical emollients are preferentially applied directly after a bath or a shower following gentle drying when the skin is still slightly moist.[32] It should be emphasized that most bath oils commercially available in Europe are practically free of proteinaceous allergens.[53] A recent study has found no evidence for a benefit of adding bath additives in addition to standard treatment regimens.[61], 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.[62]

The addition of antiseptics such as sodium hypochlorite (bleach bath) has been proven 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%.[63] 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 therapy[64] (see chapter phototherapy).

3. Antiinflammatory treatment

We **recommend** the use of topical corticosteroids (TCS) as anti-inflammatory agents.	↑↑	>75%  (24/26) Expert Consensus
We **recommend** the use of topical calcineurin inhibitors (TCI) as anti-inflammatory agents.		

We **suggest** using anti-inflammatory topical agents according to the fingertip unit rule.	↑	>75%  (23/26) Expert Consensus

We **suggest** the use of wet wraps with diluted (see background text) or low potency topical corticosteroid in acute AE.	↑	>50%  (14/22) Expert Consensus

We **recommend** TCS in AE especially for treatment of acute flares.	↑↑	100%  (23/23) Expert Consensus
We **recommend** to note and adequately address patients concerns or fears about corticosteroid side effects.		
We **recommend** using TCI particularly in skin areas with a risk of skin atrophy due to TCS application (face, intertriginous sites, anogenital area).		

We **suggest** initial treatment with topical corticosteroids before switching to a TCI to reduce the risk of skin stinging and burning.	↑	100%  (23/23) Expert Consensus

We **recommend** proactive therapy (e.g. twice weekly application) with a suitable TCS or a suitable TCI (see background text) to reduce the risk of relapse and for better disease control.	↑↑	100%  (22/22) Expert Consensus

Effective topical therapy depends on three fundamental principles: sufficient potency, sufficient dosage and correct application.[65] 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.

Aim of this chapter was to give an overview of the efficacy and safety profile of the current topical therapies and provide a summary of emerging topical treatments for AE.

Based on a systematic search in common databases we conducted a revision of the existing consensus papers.

The applied amount of anti-inflammatory topicals 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. The proactive therapy is defined as a combination of predefined, long-term, anti-inflammatory treatment applied usually twice a week to previously affected areas of skin in combination with liberal daily use of emollients on the entire body. Additionally, it is marked by a predefined appointment schedule for clinical examinations.[66] 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 the proactive management is usually adapted to the severity and persistence of the disease.[67]

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. The use of 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.[68-71]

Wet wraps can be conducted with topical corticosteroid creams and ointments.[72] 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.

3.1. 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 the needs (pruritus, sleeplessness, new flare).[73, 74] The lipophilicity and the low molecular weight of TCS allows 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).[75] This classification is used across Europe, except for France, where this classification is similar but in an inversed ranking. This classification is used throughout this guideline. In contrast, the US-American classification differs and recognises 7 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, long term

When choosing a TCS beside 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 routinely be used. 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, neck) should be restricted to mild-to-moderate TCS (class I and II).[76]

With mild disease activity a small amount of TCS twice to thrice weekly (monthly amounts in the mean range of 15 g in infants, 30 g in children and up to 60–90 g in adolescents and adults, roughly adapted to affected body surface area), associated with a liberal use of 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 significantly reduction of AE-flare recurrence. Outside of the context of clinical trials, similar experience also exists for other class III and even class II TCS.[73, 74, 77]

Safety

Potent and very potent TCS of group III and IV may be absorbed systemically and can more likely cause depression of adrenal function than group I and II treatments, but their systemic effects will decrease more quickly due to more rapid restitution of the skin barrier, and cases of significant adrenal suppression from long-term TCS use are very rare.[78] Ghajar et al. reviewed 9 studies (n=371) measuring serum cortisol levels after two weeks of TCS application. Low to moderate potency TCS showed no risk

for adrenal suppression after short-term use.[79] Fishbein et al. reviewed 12 studies with 2224 children using TCS. In 4 of 157 measured participants (3%) mild adrenal suppression was reported.[80]
Side-effects of TCS comprise a variety of skin changes mostly in the sense of skin atrophy – except from contact allergy to corticosteroid substances. The skin changes manifest as thinning of the skin, development of teleangiectasia (rubeosis steroidica), spontaneous scars (pseudo-cicatrices stellaires), ecchymosis, striae distensae (stretch marks) and hypertrichosis.[81]
A review of 11 trials showed a prevalence rate of burning, pruritus, irritation or warmth after TCS application ranging from <1% to 6%.[82]
In infants, inappropriate use of high potency TCS in the diaper area can lead to granuloma gluteale infantum or even iatrogenic Cushing's disease.[83]
The risk of ocular complications by TCS seems to be low. The application of TCS to the eyelids and periorbital region in adults with AE, even over longer periods of time, was not associated to the development of glaucoma or cataracts.[84] However, there are single case reports of increased intraocular pressure after topical application of TCS, therefore physicians should be aware of this potential risk.[85, 86]
In the face, rosacea-like perioral dermatitis can be induced by inappropriate, long term use of potent or super-potent TCS (group III, IV) and the skin can become dependent on TCS use ("red face syndrome" or "corticosteroid addiction syndrome"). It is characterized by persistent erythema, burning and stinging sensation and it has been reported mostly on the face and genital area of women.[87]

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 evaluation of 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.[88, 89] 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 anti-inflammatory treatment early and use them intensively during the acute flares.[65]

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 pediatric patients with severe AE, the efficacy and safety profile of pimecrolimus cream 1% combined with fluticasone were similar to that of fluticasone alone.[90] 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 in 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).[67]**Special considerations**

Patient fear of side effects of corticosteroids (corticophobia) is quite common and should be recognized (e.g.. by TOPICOP score[91]) and adequately addressed to improve adherence and avoid undertreatment.[92-94]

In pregnancy and lactation lower potency TCS should be used where possible (see chapter Pregnancy, breastfeeding, and family planning).

3.2. 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. TCIs 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 TCS.[95, 96] TCI are a first line therapy for sensitive areas where TCS use is likely associated with side effects or in areas where TCS had already caused side effects. The efficacy of both formulations has been demonstrated against vehicle in clinical trials for short-term (three weeks)[97, 98] and long-term use up to one year.[99, 100]

The efficacy of long-term monotherapy with tacrolimus ointment has been shown in children and adults.[101-103] In adults, long-term proactive treatment with 0.1% tacrolimus ointment has shown good effectiveness for flare prevention, similar to class III TCS.[102] 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 the quality of life (QoL) in both adults and children.[104, 105] Pimecrolimus 1% cream has been studied in infants and children in a combination regimen with TCS[106, 107], the latter being given if a flare occurred. Less data are available for children under 2 years of age.[108, 109] 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, long term

The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a potent corticosteroid (class III)[101, 102, 110], and 0.1% tacrolimus ointment is clearly more effective than 1% pimecrolimus cream.[103]

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.[104, 105]

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 on 10-year tacrolimus and 5-year pimecrolimus studies, demonstrating the safety of this anti-inflammatory treatment in daily practice.[111, 112]

None of the TCI induces skin atrophy.[113, 114] This favors 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.[115]

The most frequently observed side effect is transient warmth, tingling or burning sensation at the application site, which may last up to 1 h.[90, 102] However, this side effect typically vanishes within a few days.[116] Some patients also experience a transient worsening of their AE. These side effects are more common with tacrolimus ointment than with pimecrolimus cream, in particular when they are applied on acutely inflamed skin. In some patients they are severe enough to induce prompt treatment discontinuation. Initial treatment with TCS should thus be considered in patients with an acute flare to minimize these site reactions.[67] In some patients intake of alcohol can trigger transient but marked facial flushing, this innocent but annoying side effect is very inconsistent even in the same patient.

Generalized viral infections such as eczema herpeticum or eczema molluscatum have been observed during TCI treatment in some studies[117, 118], but a high number of clinical trials failed to demonstrate an increased frequency or showed only a transient increase in viral infection.[117, 119-121]

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.[122] 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.[123] The application of TCI is not associated with an increased risk for non-melanoma skin cancer, other malignancies or photocarcinogenicity.[112, 124-128] In a retrospective cohort study with more than 90,000 participants and over ten years, no increased risk of basal cell carcinoma or squamous cell carcinoma was observed.[129] 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.[130] A recent paediatric prospective observational cohort study (APPLES, n=7,954) 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 cyclosporine (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 phototherapy should be avoided.[131]

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 the observational study evidence has not found a convincing association between long-term TCI use and cancer development.[123]

Monitoring

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

Special considerations

Though TCIs are not approved in pregnancy and lactation (see chapter Pregnancy, breastfeeding, and family planning), off-label use in pregnancy and lactation is possible as there is no teratogenic potential reported for the entire substance class.[132]

3.3. Topical phosphodiesterase 4 inhibitors

Mechanisms of action and efficacy

The topical phosphodiesterase 4 (PDE-4) inhibitor, crisaborole, is approved for treatment of mildtomoderate AE in patients 2 years of age and older in the United States of America, Canada, Australia, Israel and Hong Kong. Crisaborole has been approved in the European Union in 2020 but is not commercialized in the European market.
The inhibition of PDE-4 leads to increased levels of intracellular cAMP, which results in a reduction of inflammatory cytokines.[133, 134] Several studies have reported anti-inflammatory and anti-pruritic effects of crisaborole in AE.[135, 136] A systematic review by Fahrbach et al. with nine randomized controlled trials confirmed the efficacy of crisaborole.[137] However, only three studies provided baseline EASI and none provided SCORAD measurement. In the pivotal studies, efficacy was only assessed by Investigator Static Global Assessment (ISGA).[138] Therefore, a direct comparison of the efficacy of crisaborole against TCI or TCS is currently not possible. Based on available data the efficacy of PDE-4-inhibitors seems to be similar to mild TCS or pimecrolimus, however further studies are needed.

Safety

Reported side-effects of crisaborole were short-term application-site pain, burning or stinging.[138] Also the long-term safety profile over 48 weeks appears to be favorable.[139]

Special considerations

Other topical phosphodiesterase 4 inhibitors under investigation include Lotamilast (RVT-501) and Difamilast (OPA-15406).[140-142]

3.4. 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.[143] Despite these promising results, the clinical development programme of tofacitinib has been stopped. Delgocitinib has been approved for the use in AE in Japan.[143, 144] In a 4-week study the selective JAK-1 and JAK-2 inhibitor ruxolitinib showed a similar or even higher efficacy in mildtomoderate AE compared to triamcinolone cream (group III TCS), and has recently been approved in the US. [145] Other JAK inhibitors with similar or different selectivity (brepocitinib) are in the pipeline for topical therapy, but none is currently licensed in Europe.

Further upcoming therapies include tapinarof, an aryl hydrocarbon receptor agonist, which showed greater efficacy in AE treatment than vehicle twice daily after 12 weeks.[146]

The transient receptor potential vanilloid 1 (TRPV1) antagonist, PAC-14028, was investigated in a phase IIb study in patients with mild-to-moderate AE and showed a significantly higher reduction in IGA than vehicle cream. Although there was an improvement in AE according to SCORAD and EASI, the effects of PAC-14028 were not statistically significant compared to the vehicle.[147]

4. Antimicrobial treatment

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

4.1. Anti-bacterial treatment

We **recommend** a short course of systemic antibiotics only in AE patients with extensive clinically superinfected lesions.	↑↑	100%  (25/25) Expert Consensus
We **suggest** against the long-term application of topical antibiotics, due to the risk of resistance development .	↓	
We **suggest** that topical anti-inflammatory treatments are continued during the treatment of Staphylococcus aureus superinfection episodes.	↑	

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.[148] 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.[149] 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 T cell activation of superantigen-specific and allergen-specific T cells, the expression of IgE anti-staphylococcal antibodies and increased expression of IL-31 which leads to pruritus and subsequent scratching.[149, 150] Scratching favors binding of *SA* to the skin, and the increased amount of *SA* derived ceramidase aggravates the skin barrier defect. Moreover, superantigen production increases expression of alternative glucocorticoid receptors that do not bind to topical corticosteroids, which leads

to treatment resistance.[151] 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.[151]

A Cochrane review by George et al.[152] with 41 studies and 1,753 participants assessed the effect of different interventions to reduce SA on the skin in people with AE. Four studies evaluated oral antibiotics versus placebo. No difference was found in the global severity assessment (RR 0.80; 95% CI 0.18 to 3.50; 2 RCTs; GRADE: low-quality) and little to no effect was reported for QoL (MD 0.11, 95% CI -0.10 to 0.32; 1 RCT; GRADE moderate-quality). Fourteen studies compared topical corticosteroids plus antibiotic with topical corticosteroids alone. Steroids/antibiotics combination participant may have a slightly greater improvement in the global signs and symptoms (RR 1.10, 95% CI 1.00 to 1.21; 3 RCTs; GRADE: low-quality). For QoL, little to no effect was found (MD -0.18, 95% CI -0.40 to 0.04; 1 RCT GRADE: moderate-quality). For bleach baths versus placebo or bath emollients, no difference was reported in the global improvement at one month follow-up (RR 0.78; 95% CI 0.37 to 1.63; 1 RCT; GRADE: low-quality) and little to no effect was documented for QoL (MD 0.90; 95% CI -1.32 to 3.12; 1 RCT; GRADE: moderate quality). This corresponds to recent data showing no antimicrobial effect in vitro of diluted bleach baths.[153]

For all three interventions adverse events leading to withdrawal of treatment were rare and evidence was very low quality. For antibiotic resistance, no significant difference was demonstrated between intervention groups and placebo but results remain uncertain because quality of evidence was very low.

Eight randomized controlled trials evaluated treated textiles (as silver) versus placebo, studies were not pooled due to heterogeneous design but no clear advantage was reported. Juenger et al.[154] found no effect in the overall disease control of AE in the silver textile group compared with non-silver textile (RR 2.40; 95% CI 0.91 to 6.36; RoB: high) and Gauger et al.[155] reported no significant difference between groups in the quality of life questionnaire (RoB: high). For summary of findings tables (modified), see appendix III.

4.2. Anti-viral treatment

We **recommend** to treat eczema herpeticum without delay using systemic antiviral therapy, such as aciclovir.	↑↑	100%  (25/25) Expert Consensus
We **recommend** to perform vaccinations in line with national guidelines.	↑↑	

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.[156]

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 lymphadenopathy 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). Pre-treatment 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.[157] Mainstay of EH therapy is systemic treatment with aciclovir or valaciclovir.[158] Treatment should be started immediately, once the clinical diagnosis is made.[36]

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 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.[159] Moreover, in children with AE, immune response to VZV vaccine is comparable to healthy children.[160] 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.[161] 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.[49] Topical treatment of AE with TCS should be continued during MCV infection.

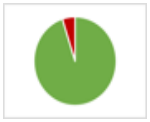
Eczema vaccinatum (EV) is a complication of smallpox vaccination known to occur in AE patients. The vaccinia virus disseminates and causes an extensive rash and severe systemic illness with a mortality rate estimate at 5-40%.[162] Therefore, smallpox vaccination is contraindicated in patients with a history of or currently active AE.[163] The existence of an attenuated vaccine (Modified Vaccinia Ankara virus) and three antiviral drugs, in addition to vaccinia immunoglobulin, provides means of preventing or treating

EV.[164, 165] Should a smallpox outbreak necessitate an emergency mass vaccination, the choice of vaccination strategies, such as ring or mass vaccination, has to be determined by policymakers.

Eczema coxsackium (EC) is a disseminated form of coxsackie virus infection mostly occurring in children with active AE lesions.[166] 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).[167] This rash may be confused with bullous impetigo or eczema herpeticum. Symptomatic treatment includes use of topical corticosteroids and wet wrap therapy.[168, 169]

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.

4.3. Anti-fungal treatment

We **suggest** topical or systemic antifungal therapy in some patients with AE, mainly in those suffering from the "head and neck" variant of AE. and with demonstrated IgE-sensitization to *Malassezia spp*.	↑	>95%  (23/24) 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 pro-inflammatory cytokines including IL-4, IL-13 and-IL 17.[170-172] Several randomized, placebo controlled trials investigated the benefit of topical or systemic antifungal treatment for AE patients.[173-175] The ambiguous results of these clinical trials might be attributed to selection bias. It can be speculated that antifungal therapies are more effective in certain subgroup of AE. It seems for example that antifungal therapy shows beneficial effects in patients with a head-neck-type distributed AE and detectable IgE-mediated sensitization against Malassezia.[176] It has also been shown that sensitization against this skin-colonizing yeast can correlate with disease activity.[177] The most common class of antifungal drugs prescribed for AE patients are azoles such as ketoconazole and itraconazole which have also some anti-inflammatory properties.[174] 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 IgE-sensitization to Malassezia spp.

5. Antipruritic treatment

Itch is the most important clinical symptom in AE with particular impact on emotional dimensions of perception as compared to 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. There is only a limited number of studies that specifically assessed the antipruritic effect of treatment modalities in AE. The treatment of itch in AE requires a multi-dimensional approach treating itch itself, but also the contributing factors, such as the dry skin and skin inflammation.

5.1. Anti-pruritic effect of anti-inflammatory treatment

The anti-inflammatory agents, both topical and systemic ones, reduce skin lesions and significantly relief itch. Although topical corticosteroids do not act as direct antipruritic agents,[178] several studies described the anti-inflammatory effect of topical corticosteroids in AE, in which pruritus was one parameter among others studied.[179]

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 to vehicle application.[179]

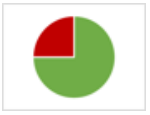
Crisaborole was shown to be effective in reducing itch in mild-to-moderate AE patients. Reszke et al. in their review consider that patients receiving crisaborole 2% ointment experienced pruritus relief at day 29 more commonly than patients receiving vehicle.[180] Furthermore, crisaborole was more likely to provide antipruritic response at the earliest assessment on day 2 and early improvement of pruritus at day 6 than vehicle.[180] However, crisaborole is not available on the European market.

Dupilumab as systemic anti-inflammatory agent showed high effectiveness in reducing itch in AE patients. All the studies confirmed the efficacy of dupilumab in terms of improvement of skin lesions and alleviation of pruritus.[181-184] Similar data exists for other systemic drugs recently licensed for AE treatment, such as tralokinumab, abrocitinib, baricitinib and upadacitinib (see chapters Biologics and JAK-Inhibitors). [185-188]

A meta-analysis of 1505 patients with moderate-to-severe AE revealed that dupilumab started to unveil its antipruritic properties by days 2 and 5 in adults and adolescents, respectively. The response increased over time and was sustained until the end of the studies (up to 1 year).[182]

5.2. Anti-pruritic treatment

Polidocanol

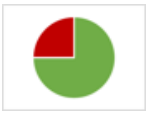
We **cannot make a recommendation** on the use of polidocanol in itch treatment in AE.	**0**	>75%  (16/17) Expert Consensus

Case series described the efficacy of a combination of the anaesthetic polidocanol and 5% urea.[189] In children with AE, the combination showed a pruritus improvement of 30% in comparison with an emollient.[190] Polidocanol is not licensed for AE in Europe, but OTC products are available.

Capsaicin

Capsaicin is a naturally occurring alkaloid and the principal pungent of hot chilli peppers. Capsaicin binds to the TRPV1 ion channel, which is present on many itch-mediating C-fibres. Capsaicin has been advocated to be antipruritic in various dermatoses. Concerning AE, experimental studies[191] and case series[192] report on clear itch reduction. However, the practical treatment and updosing are challenging, and no controlled study has been published.

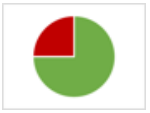
Topical antihistamines

We **recommend against** topical antihistamines in itch treatment in AE.	↓↓	>75%  (17/18)[1] Expert Consensus

[1] 1 Abstention

5% doxepin cream exhibited antipruritic effects in three controlled studies in AE; one RCT assessed the efficacy of cromoglycate 4% lotion.[179] The meta-analysis of those studies documented that the use of topical antihistamines markedly reduced itch of AE by 27% in patients in comparison with the vehicle. However, topical doxepin therapy is not licensed and not used in any European country due to an increased risk of contact allergy, especially when the treatment exceeds eight days.

UV therapy

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

[1]2 Abstention

UV phototherapy relieves pruritus in AE, which has been demonstrated in several studies. A systematic review of 19 available RCTs suggests the usage of narrowband UVB and UVA1 as the most effective in the treatment of AE, including reduction in itch intensity.[193] A recent study by Jaworek at al.[194] documented that narrowband UVB reduces itch in AE patients significantly better than ciclosporine.[194] There is no 'anti-itch-specific' data for UV phototherapy available, which would differ from the general recommendations for UV phototherapy treatment of AE.

Systemic antihistamines

We **suggest against** using first generation systemic antihistamines as a longterm treatment for itch in AE.	↓	100%  (22/22) Expert Consensus
We **suggest against** using second generation systemic antihistamines as a treatment for itch in AE.	↓	>75%  (13/15)[1] Expert Consensus

[1] 1 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.[195-203] A recent Cochrane review did not find consistent evidence that H1 AH treatments are effective as 'add-on' therapy for AE when compared to placebo.[204] The certainty of evidence for this comparison was of low and moderate quality.[204] It seems that only fexofenadine may lead to small improvement in patient-assessed pruritus (mean difference (MD) -0.25, 95% CI -0.43 to -0.07; n = 400) and a greater reduction in the ratio of physician-assessed pruritus area to whole body surface area.[204, 205] However, these reductions may not be clinically meaningful[204]. In general, AH are safe to use, also for a long period of time.[206] There is limited data for the antipruritic effect of AH (H1 antagonists) in AE in general, and the effect of both first and second generation AH on pruritus in patients suffering from AE is very limited. The clinical value of systemic antihistamines for the anti-pruritic treatment of AE is not supported.
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. [5, 207, 208]

Opioid receptor antagonists

The μ-opioid receptor antagonist nalmefene was applied in smaller randomized, controlled studies in AE. A dosage of 10 and 20 mg each once per day showed significant relief of pruritus in three studies.[209-211] In open-label trials and one double-blind, placebo-controlled study trial, the only orally active μ-opioid antagonist naltrexone 25–150 mg per day showed considerable antipruritic effects.[212, 213] Common adverse events include anxiety, arthralgia, dizziness, drowsiness, fatigue, vomiting and headache. None of these substances is currently licensed for the treatment of AE itch. The benefit-risk ratio is unfavourable.

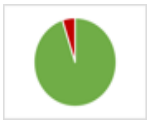
Selective serotonin reuptake inhibitors

We **suggest against** the use of selective serotonin reuptake inhibitors as itch treatment in AE patients.	↓	100%  (20/20) Expert Consensus

The antipruritic effect of the selective serotonin reuptake inhibitors paroxetine and fluvoxamine was investigated in an open-label trial in dermatological patients. A few patients with pruritus due to AE were included, who responded with considerable reduction in pruritus. In these patients, the pruritus was reduced about half in intensity (maximal antipruritic effect score, 45.0 + /-7.1%).[214] Although the evidence of antipruritic activity of selective serotonin reuptake inhibitors in AE is very low, these agents might be used as second or third line therapy in other types of chronic itch.

Adverse events include constipation, diarrhoea, dizziness, drowsiness, ejaculatory and erectile dysfunction, decreased libido, insomnia, nausea and headache. The risk–benefit ratio of SSRI is highly unfavourable.

6. Phototherapy and Photochemotherapy

We **recommend** narrowband UVB and medium-dose UVA1 for AE patients with moderate-to-severe AE.	↑↑	>95%  (24/25) Expert Consensus
We **suggest** the use of narrowband UVB or UVA1 in *children and adolescents* after the assessment of skin type (see background text), but frequent and/or protracted treatment cycles should be avoided.	↑	>95%  (24/25)[1] Expert Consensus
We **suggest** that other phototherapy modalities (balneophototherapy, UVAB, BB-UVB, UVA) are to be considered as a second choice.	↑	100%  (25/25) Expert Consensus
We **suggest** that PUVA therapy is only used, when previous treatment cycles with other phototherapies were ineffective or when approved drug treatments are contraindicated, ineffective or have caused side effects.	↑	100%  (25/25) Expert Consensus
We **suggest** co-treatment with topical emollients during phototherapy.	↑	100%  (25/25) Expert Consensus
We **recommend against** the use of prolonged or repeated treatment cycles and maintenance regimens with all phototherapy modalities.	↓↓	100%  (24/24) Expert Consensus

[1] 1 abstention

We **recommend against** the use of all phototherapy modalities in patients with a history of skin cancer and with an increased risk of skin cancer (including photodamaged skin and those on systemic immunosuppressants (see background text)).	↓↓	100%  (25/25) Expert Consensus

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

Photo(chemo)therapy can be used in patients with moderate-to-severe AE recalcitrant to topical therapy. Background information on photobiology, UV modalities and practical aspects can be found in Appendix I.

The systematic review of Garritsen et al. investigated the efficacy and safety of treatment with photo(chemo)therapy in AE patients up to 26 October 2012.[193] Only RCTs were included. No meta-analysis could be performed due to methodological heterogeneity. Nineteen studies were included with a total of 905 adult participants (sample size range 9 to 180), treatment duration varying between 10 days and 40 weeks, and with a follow-up up to 1 year (mean 15.3 weeks).

Studies on BB-UVB (4 studies, n=120),[215-218] NB-UVB (6, n=188),[219-224] UVA (3, n=84),[217, 218, 223] UVA1 (9, n=259),[219, 221, 222, 225-230] cold-light UVA1 (1, n=50),[230] UVAB (7, n=200),[215, 218, 227, 228, 230-232] full-spectrum light (1, n=20),[233] PUVA (2, n=29),[220, 229] visible light (1, n=20),[216, 223] and balneophototherapy (1, n=90) were included.[224] Concomitant emollient use was permitted in all the RCTs. Detailed tables including patient and treatment characteristics, study outcomes and GRADE assessment can be found in the paper of Garritsen et al.[193] Below is a summary of the results.

Three studies of low[222] to moderate quality[219, 221] compared medium dose (MD) **UVA1 with NB-UVB**; no significant difference was found in clinical signs (apart from 1 clinical sign instrument (Leicester Sign Score) in favour of NB-UVB in 1 RCT of low-quality[222]).

Three studies of low[228], moderate[227] and high[230] quality found **UVA1** [one medium dose (MD) and two high dose (HD) protocols] to be significantly more effective than **UVAB** regarding clinical signs and symptoms.[227, 228, 230] No significant difference was found between **MD-UVA1** and **HD-UVA1** after stop of treatment and after 6 months of follow-up in two studies of very low[226] (pilot study) and moderate quality (intrapatient, side to side comparison study).[225]

One low-quality study showed more improvement in clinical signs and symptoms of **NB-UVB** versus **UVA and visible light** up to 3 months of follow-up (no statistical significance mentioned).[223]

One low-quality study showed **UVB** to be significantly more effective compared to placebo **visible light** for clinical signs and symptoms.[216]

One study of very low quality[218] and one of low quality[215] showed **UVAB** to be significantly more effective compared to **UVA** (clinical signs) and **BB-UVB** (clinical signs and symptoms) respectively. Another study of low quality showed **UVA** to significantly reduce clinical signs compared to **BB-UVB**.[217] **UVAB** combined **with topical corticosteroids** led to significantly greater reduction in clinical signs and symptoms than UVAB alone in a moderate-quality study.[232] **UVAB** compared to **ciclosporin** was significantly less effective on the short-term for clinical signs and QoL.[231]

PUVA turned out to be significantly more effective than **MD-UVA1** in clinical signs and duration of remission in one low-quality study.[229] Between **PUVA** and **NB-UVB** no significant difference was demonstrated in clinical signs after treatment nor after follow-up up to 1 year in one very low-quality study.[220]

Full-spectrum light (320-5000nm) versus controls with emollients significantly reduced clinical signs up to a follow-up of 4 weeks in one very low-quality study.[233]

Balneophototherapy (saltwater bath plus NB-UVB) was significantly more effective than **NB-UVB** for clinical signs up to 6 months of follow-up in a low-quality study.[224]

Based on this systematic review conclusions must be drawn carefully, because of small and heterogeneous studies, high degrees of bias and varying levels of evidence. In terms of efficacy most evidence is available for MD-UVA-1 and NB-UVB. No difference was found between HD-UVA1 and MD-UVA1; more evidence was available for MD-UVA1. UVAB was more effective than UVA and BB-UVB, but not compared to UVA1. Other options are PUVA, full-spectrum light and balneophototherapy, but studies were small and of low quality. No suitable RCTs on heliothalassotherapy or Goeckerman therapy (coal tar plus UVB) were found.

Of the two RCTs retrieved from the additional search, the first compared **UVA** (n=30) with **UVB** (n=30) thrice weekly for a maximum of 12 weeks, with a follow up of 3 months, in moderate-to-severe AE patients.[234] Both modalities had a similar effect on reduction in clinical signs. The second evaluated **HD-UVA1** (130 J/cm^2) versus **MD-UVA1** (60 J/cm^2) five times weekly for 3 weeks in 27 severe adult AE patients.[235] Patients with skin type III-IV responded significantly more to HD-UVA1 than MD-UVA1 concerning clinical signs; patients with skin type II showed no difference between these two.

No evidence on efficacy of phototherapy in acute versus chronic AE was found, and no RCTs for children were found. Apart from some (mostly retrospective) case series,[236-242] two non-randomized studies have been published. In a comparative non-randomized study, 29 AE children and adolescents, aged 3-16 years, were treated with NB-UVB phototherapy for 12 weeks and compared with 26 patients who chose not to undertake treatment.[243] There was a 61% reduction in mean Six Area, Six Sign Atopic Dermatitis (SASSAD) severity score at week 12 in the NB-UVB cohort compared with an increase of 6% in the unexposed cohort. An open-label trial without control group assessed the effectiveness and safety of NB-UVB phototherapy in 30 AE children, aged 4-14 years. There was a significant reduction in severity at the end of treatment compared to baseline; this effect maintained during 2 years of follow-up.[244]

Concluding this section, we must emphasise 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.[245]

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

In the RCTs included in the systematic review of Garritsen[193] and in the additional two RCTs[234, 235] no serious side-effects during the treatment and up to 1 year of follow-up were reported. Short-term side-effects (up to 1 year of follow-up) include xerosis cutis, erythema and burning, pruritus (UVA1 and full-spectrum light), gastrointestinal diseases (balneophototehrapy), exacerbations of AE (UVA, NVB-UVB, visible light, full-spectrum light), folliculitis (UVA1, PUVA), and photo-onycholysis (PUVA). The open-label

trial performed in children reported grade II erythema, reactivation of herpes labialis and chickenpox as side-effects. Follow-up up to 2 years did not show any significant side-effects.

However, 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 patients' cohorts and with prolonged follow-up.

These studies are available for patients treated with UVA1,[246] BB-UVB and NB-UVB for other indications, mainly psoriasis, and they did not show increased risks of basal cell carcinoma, squamous cell carcinoma and melanoma.[247, 248] However, due to the lack of adequate prospective studies a follow up of patients who underwent repeated and protracted treatment cycles is recommended, particularly in lighter skin types.[249] The cancerogenic risk of PUVA is well demonstrated in psoriatic patients, and therefore caution is recommended also in AE patients.[249,250, 251] 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 cyclosporine and azathioprine, phototherapy is not recommended based on their risk of co-carcinogenicity (see chapter Conventional systemic drugs). There are few papers available on combination therapy and the long-term safety in psoriatic patients;[252, 253] no papers were found specifically for AE. (see separate appendix)

7. Introduction to systemic treatment

The area of systemic therapy of AE has flourished during the last few years, as many new substances are marketed, licensed, or in the last step of clinical development. The licensing programs of the various new biologics and small molecules are providing much better levels of evidence than what is available for the longer existing drugs.

By tradition, systemic therapy of AE is deemed necessary if the signs and symptoms of AE cannot be controlled sufficiently with appropriate topical treatments and UV-light therapy. Systemic therapy can also be useful to reduce the total amount of TCS in patients who need large amounts of potent TCS for vast body areas over prolonged periods to control their AE.

Candidates for systemic treatment may be either patients with a high composite score such as a SCORAD above 50 (scale definition), or to patients clinically failing to respond to an appropriately conducted topical therapy (functional definition), or patients unable to participate in normal daily life activities whilst following an adequate treatment regimen (social definition).

Local regulations may necessitate the use of other scores such as physician-based scores (e.g. EASI) in combination with patient reported outcomes (e.g. DLQI). Many other scores exist summarized and assessed by the HOME initiative that may also serve as a base to classify disease severity.[254]

It must be highlighted that the indication to systemic treatment is a patient individual decision, and that a signs-only score, such as EASI, is not an adequate tool to discriminate for providing or declining systemic therapy to an individual patient.

100 % agreement

Before starting systemic treatment, it is important to rule out relevant differential diagnoses such as cutaneous T-cell lymphoma and in selected cases primary immunodeficiency syndromes [255]), and to ascertain that potential trigger factors such as allergic contact dermatitis, and behavioural as well as educational reasons for poor responses.

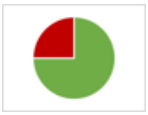
Until recently, rather broad acting immunosuppressants, such as systemic corticosteroids (SCS), ciclosporin (CyA), azathioprine (AZA), mycophenolate mofetil (MMF), enteric-coated mycophenolate sodium (EC-MPS) and methotrexate (MTX)) were the only systemic treatment options available for difficult-to-treat AE. Most were not licensed for this indication. These drugs may roughly be divided in two groups: SCS and CyA have a rapid onset of action and can be used to treat flares of AE or to bridge the time until onset of action of slow acting systemic immunosuppressants such as MTX, AZA and MMF/EC-MPS. The kinetics of the novel januskinase inhibitors baricitinib (Bari), abrocitinib (Abro) and upadacitinib (Upa) place these agents in the fast-acting group, whereas the Th2-blocking agents dupilumab (Dupi), tralokinumab and lebrikizumab, as well as the IL31-receptor blocking agent nemolizumab (Nemo) need some weeks to reach full efficacy.

Special considerations should be taken during the running COVID-19 pandemic, as indicated by recommendations from the European Taskforce for Atopic Dermatitis.[256, 257] Particular caution is required where patients receive combined systemic therapy.

The following recommendations for systemic drugs are based on expert opinions, the living systematic review by Drucker et al[3], other published literature and medical considerations, and may differ from the legal licensing status and access routes, which are not uniform in European countries.

8. Conventional systemic drugs

8.1. Azathioprine (AZA)

We **suggest** using azathioprine in AE patients who are candidates for systemic treatment.	↑	>75%  (14/15) Evidence and consensus based, see Evidence Report

azathioprine: off licence; commonly used dosage
adults: 1-3 mg/kg per day
children: 1-3 mg/kg per day

Certainty of evidence[2, 3]:

Short term (8-16 weeks) vs placebo (NMA medications used in clinical practice or likely to be approved soon)

⊕⊕⊕◯ MODERATE for standardized mean difference **change in signs**

⊕⊕◯◯ LOW for standardized mean difference QoL, itch

For azathioprine versus other drugs, see Evidence Report

Mechanisms of action and efficacy

AZA is a pro-drug which is rapidly converted in vivo to the anti-metabolite 6-mercaptopurine (6-MP), following cleavage of its imidazole side chain. It is believed to exert its primary immunosuppressant effect via metabolites of 6-MP, thioguanine nucleotides (TGNs), which are subsequently incorporated into DNA, inhibiting its synthesis.[258]

The efficacy of AZA is comparable to that of MTX but lower compared to dupilumab and cyclosporine A in clearing clinical signs of AE.[259]

Randomized clinical trials report a significant superiority of AZA vs placebo, with a decrease in clinical scores such as Six Area, Six Sign Atopic Dermatitis and Scoring Atopic Dermatitis (SASSAD) by 26% to 39% after 12 weeks.[260] However, results from retrospective studies are less favorable with a percentage of AZA treatment failure varying from 30 to 57% due to adverse effects or lack of effectiveness.[261-263] An observational follow-up study of 36 adult patients with severe AE treated with MTX or AZA over a 24-week period demonstrated less improvement in subjects with filaggrin mutations (36%, 13/36) compared to those without filaggrin mutations.[260]

Long-term studies on adult patients treated with either AZA or MTX showed a relative reduction in SCORAD of 53% ($P < .01$) and 63% ($P < .01$) after 2 years, and 54% and 53% after 5 years, respectively.[260, 264] Patients with a Filaggrin mutation seemed to have slower but prolonged effects of therapy compared with patients without a mutation.[260, 264]

Dosage: acute flare, short term, long term

- off licence
- commonly used dosage
    - adults and children: 1-3 mg/kg bodyweight per day
    - If no improvement of AE occurs within 3 months, withdrawing azathioprine should be considered.
- We recommend combining AZA, as any systemic treatment with emollients and, whenever needed, topical anti-inflammatory treatment in AE patients.
- If timely thiopurine S-methyltransferase (TPMT) activity measurement is available, the following dosing of AZA has been suggested:
    - very low activity (< 2.5 per mL red blood cells [RBC]), treatment should not be started
    - intermediate activity (2.5-7.5 nmol/h/mL RBC): 0.5 mg/kg bodyweight per day for the first 4 weeks and then increase to 1.0 mg/kg bodyweight per day
    - normal activity (>7.5 nmol/h/mL RBC): 2.0 mg/kg bodyweight per day for the first 4 weeks and then increase to 2.5-3.0 mg/kg bodyweight per day

Low azathioprine doses (0.5-1.0 mg/kg bodyweight per day) for the first 4 weeks were shown to reduce gastrointestinal side-effects.[265]

If TPMT results are not available prior to starting AZA therapy, then half the standard treatment should be given for about 4-6 weeks under close monitoring of full blood count and liver profile, prior to going up the full treatment dose.

Safety

In the short and medium term, the most commonly reported serious dose-dependent effects are hepatotoxicity and myelotoxicity, together with gastrointestinal disturbances. Further, idiosyncratic hypersensitivity reactions (e.g. fever, rigours, myalgia, arthralgia and occasionally pancreatitis) may occur.[266]

Concerns have been raised about the potential carcinogenecity induced by long-term treatment with azathioprine (predominantly squamous cell skin cancer and n on-Hodgkin's lymphoma), especially if AZA is combined with other immunosuppressants regimens.[267]

Monitoring

- Baseline: Complete blood count, renal and liver profile
- TPMT activity if available.
- Screening for chronic infections (e.g. hepatitis B-/C, HIV) before therapy should be considered
- Follow up: Complete blood count, renal and liver profile twice monthly for 2 months, monthly for 4 months, then every other month and with dose increases
- Pregnancy testing before and during AZA therapy where indicated

Combination with other treatments

Concomitantly to AZA, topical therapy with corticosteroids and or calcineurin inhibitors can be applied.

Because of a potentially increased risk to develop skin cancer, AZA should not be combined with UV light (UVA, UVB, PUVA).

Special considerations

There is a theoretical risk of teratogenesis with AZA. This is based on studies in animals in which very high doses of AZA were used. However, in practice AZA has been used for over 30 years in sexually active men and women and no definite association between the drug and the incidence of foetal abnormalities has been observed. There also seems to be no effect on fertility.

According to a recent position paper by ETFAD[132], AZA use during pregnancy should be avoided as there are better options, but may be used off-label in the absence of other alternatives as continuation of treatment in women already receiving this treatment at the time of conception. According to experts' opinion of the ETFAD, the dosage of azathioprine should be reduced by 50% if it is continued during pregnancy. Initiation of azathioprine after conception is not recommend.

The use of AZA during lactation is debated. The WHO has recommended that the potential side-effects of AZA outweigh the effects and benefits of the treatment[268], and studies suggest that AZA intake during breastfeeding could increase the longterm risk of immunosuppression and carcinogenesis in the child.[269]

AZA is not licensed for the treatment of AE in children but it has proven beneficial in several retrospective pediatric case series. The main disadvantage of AZA is that it reaches its maximum treatment effect only after 3-4 months.[270]

8.2. Ciclosporin

We **recommend** using ciclosporin to achieve disease control in AE patients who are candidates for systemic treatment.	↑↑	>75%  (14/15) Evidence and consensus based, see Evidence Report

ciclosporin: in licence for ≥ 16 years
standard dosage adults: 2.5-5 mg/kg per day in two single doses
commonly used dosage children: 2.5-5 mg/kg per day in two single doses

Certainty of evidence[2, 3]:

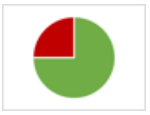
Short term (8-16 weeks) vs placebo (NMA medications used in clinical practice or likely to be approved soon)

⊕⊕⊕○ MODERATE for standardized mean difference **change in signs**

⊕⊕⊕○ MODERATE - ⊕⊕○○ LOW for standardized mean difference QoL

⊕⊕○○ LOW for standardized mean difference itch

For ciclosporin versus other drugs, see Evidence Report

We **recommend** to start with higher ciclosporin dosages in order to achieve a more rapid response in AE patients who are candidates for systemic treatment.	↑↑	>75%  (14/15) Expert Consensus

We **recommend** close follow-up for potential blood pressure elevation and signs of renal impairment in AE patients on ciclosporin.	↑↑	100%  (15/15) Expert Consensus

Mechanisms of action and efficacy

Ciclosporin inhibits T cell activation and proliferation by blocking nuclear factor of activated T cells (NFAT)-dependent cytokine production.

Ciclosporin has been approved for treatment of AE in adults in many European countries and is considered as first line option for patients with severe disease if other, novel therapies are not available or indicated. Ciclosporin is very effective for AE in both children and adults with a better tolerability in children.[271, 272] Although similarly effective in the above NMA meta-analysis evaluating trials up to 16 weeks, real life data reveal a longer drug survival of dupilumab compared to CyA after 16 months.[259, 273] In head-to-head trials ciclosporin was superior to MTX, prednisolone, IVIG, UVA and UVB, and similarly efficacious as enteric-coated mycophenolate sodium (EC-MPS).[260, 274] In the short-term treatment of AE, higher ciclosporin dosages (5 mg/kg per day) lead to a more rapid response and are more efficacious than lower dosages (2.5-3 mg/kg per day).[260] Longterm use of ciclosporin up to 1 year can be recommended based on several trials, however, their evidence is limited because of the open-label design and high dropout rates.[260]

Dosage: acute flare, short term, long term

- in licence for ≥ 16 years
- standard dosage adults: 2.5-5 mg/kg per day in two single doses
    - Acute flare, short-term: 4-5 mg/kg body weight per day
    - Long-term: 2.5-3 mg/kg body weight per day
- commonly used dosage children: 2.5-5 mg/kg per day in two single doses
    - We recommend combining CyA, as any systemic treatment, with emollients and, whenever needed, topical anti-inflammatory treatment in AE patients.

Safety

Ciclosporin has a narrow therapeutic index and requires a close follow-up for blood pressure and signs of renal impairment. To note, clinically relevant increase of creatinine seems less common than expected.[263, 272]

Monitoring

- Blood pressure, full blood count, renal and liver profile (including GGT) according to national guidelines (e.g. at baseline, 4 weeks and then 3-monthly).
- Screening for hepatitis B/C and HIV before therapy should be considered.

Combination with other treatments

Concomitantly to ciclosporin, topical therapy with corticosteroids and/or calcineurin inhibitors can be applied.

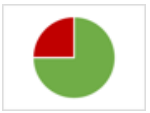
Because of a potentially increased risk to develop skin cancer, ciclosporin should not be combined with UV light (UVA, UVB, PUVA).

Special considerations

Ciclosporin has been shown to be effective, safe and well tolerated in children and adolescents.[271, 275]

Ciclosporin can be considered in pregnant woman with severe AE. So far, no increased risk of congenital malformations or fetal death compared to the background populations have been reported. An increased risk of low birthweight cannot be ruled out.[132] Where systemic therapy is likely to be needed throughout pregnancy, ciclosporin is first choice therapy.[132]

8.3. Systemic glucocorticosteroids

We **suggest** using systemic glucocorticosteroids *only* as rescue therapy for acute flares in AE patients.	↑	>75%  (14/15) Expert Consensus

systemic glucocorticosteroids: general licence for adults and children;
starting dose 0.5mg/kg per day; dosage maximum: 1 mg/kg per day

We **recommend against** the long-term use of systemic glucocorticosteroids in AE patients.	↓↓	100%  (15/15) Expert Consensus

Mechanisms of action and efficacy

Glucocorticoids are a class of steroid hormones that bind to the glucocorticoid receptor. The activated glucocorticoid receptor complex upregulates the expression of anti-inflammatory proteins and suppresses the expression of pro-inflammatory proteins, leading to broad anti-inflammatory property.[276]

There are only few studies in adult and paediatric AE patients, despite the regular use of systemic glucocorticosteroids in clinical practice. In studies conducted on children and adults, systemic glucocorticosteroids do not induce long-term remission and swift rebound is common. Systemic glucocorticosteroids have significantly inferior efficacy than ciclosporin.[271, 277]

Dosage: acute flare, short term, long term

- Acute flare: Starting dose is usually 0.5 mg/kg bodyweight per day. Treatment should be discountinued or tapered as soon as possible.
- Short-term and long-term: no relevant dosing
- We recommend combining systemic glucocorticosteroids, as any systemic treatment, with emollients and, whenever needed, topical anti-inflammatory treatment in AE patients.

Safety

Systemic glucocorticosteroids have a wide therapeutic index. Toxicity is related to the mean dose, cumulative dose and duration of use. At high doses and with long-term use (typically >0.5mg/kg/day) important side effects include skin atrophy, weight gain, sleep disturbance, mood changes, hyperglycaemia or new onset diabetes, peptic ulcers/gastritis, osteoporosis, and increased susceptibility to infections.[278] In particular with long-term use, patients can also develop adrenal suppression and

together with a high risk of rebound flares when tapering the treatment dose, cessation can be challenging. Systemic glucocorticosteroids must therefore be avoided as a long-term treatment in adults and children. Even a fairly high dose can simply be stopped without tapering when used for no longer than three weeks.[279]

Monitoring

No standard set of variables are recommended when used for acute rescue therapy, but many patient individual needs for monitoring may apply.

Combination with other treatments

There are none of the other treatments in AE that are contraindicated when using systemic glucocorticosteroids.

Special considerations

Treatment of acute flares of AE with oral glucocorticosteroids is moderately effective.[271, 277]

Systemic glucocorticosteroids have an unfavourable risk/benefit ratio for the long-term treatment of adult and paediatric AE.

8.4. Methotrexate

We **suggest** using methotrexate in AE patients who are candidates for systemic treatment.	↑	>75%  (14/15) Evidence and consensus based see, Evidence Report

methotrexate: off licence; commonly used dosage
adults: initial dose: 5-15 mg per week; maximum dose: 25 mg per week
children: 0.3–0.4 mg/kg per week; maxium dose: 25mg per week

Certainty of evidence[2, 3]:

Short term (8-16 weeks) vs placebo (NMA medications used in clinical practice or likely to be approved soon)

⊕⊕◯◯ LOW for standardized mean difference change in signs, QoI, itch

For methotrexate versus other drugs, see Evidence Report

Mechanisms of action and efficacy

MTX is a folic acid antagonist that impedes cell division, DNA/RNA synthesis and repair and protein synthesis, altogether suppressing the activity of the immune system. Although its exact action in AE is not fully understood, inhibition of the JAK/STAT pathway has been proposed.[280]

MTX has been used in the treatment of moderate and severe AE for years, but only a limited number of non-randomised controlled trials have examined the effect and treatment regimens. Consequently, recommendations have been primarily based on case series and expert consensus[281-283], one controlled study comparing MTX with AZA in adults[284] and an open-label randomised multi-centre study in children.[285] Altogether these studies support that MTX can be considered moderately effective, relatively safe, and well-tolerated treatments for severe AE both in children and adults - findings also in keeping with recent retrospective studies.[286-288] The efficacy of MTX was comparable to AZA and lower than dupilumab and ciclosporin in clearing clinical signs of AE at week 16. However, there are no long-time follow up head-to-head studies available for further comparison.[259] The onset of action takes several weeks and peak efficacy is seen after months, but speed of treatment effect onset depends on the dosing regimen.[281-283] One adult study suggests that patients who do not benefit from a moderate weekly dose (10–15 mg) of MTX over a three-month treatment period will probably not benefit from an increased dosage. However, slow gradual up-dosing of MTX might underestimate the therapeutic potential of the drug in AE. In children 0.4mg/kg/week is recommended, which is significantly higher than dosing in adults.[281] 25mg per week are the widely used maximum treatment dose for adult and paediatric AE patients.

Dosage: acute flare, short term, long term

- off licence
- commonly used dosage

- adults: initial dose: 5-15 mg/ per week; maximum dose: 25 mg/ week
- children: 0.3–0.4 mg/kg per week Acute flare and short-term: no relevant dosing

- Oral and subcutaneous delivery are considered equivalent options of administration. For patients in whom MTX 15 to 25 mg orally once weekly is ineffective or poorly tolerated, a trial of subcutaneous MTX administration is an alternative.
- We recommend combining MTX, as any systemic treatment, with emollients and, whenever needed, topical anti-inflammatory treatment in AE patients.
- Concomitant use of folic acid should be considered to reduce gastrointestinal and other side-effects related to the folic acid antagonistic effect of the drug.[289]

Safety

As MTX is a commonly used drug in dermatology, the safety profile is well recognized, with nausea, fatigue and raised liver enzymes as main side effects, while pancytopenia and idiopathic pulmonary fibrosis is of key concern but only very rarely seen.

MTX is generally well tolerated and is considered safe for long-term treatment, based on experience and multiple studies including both adults and children suffering from psoriasis and rheumatologic disease.[290, 291]

Monitoring

Complete blood count, renal and liver profile before and every 4 weeks for the first 3 months or, after increasing the dose, then every 8-12 weeks.

Type III procollagen peptide (PIIINP) should be monitored according to national and local guidelines when available. Fibroscan or liver biopsy when necessary in selected cases.

Screening for chronic infections (e.g. hepatitis B-/C, HIV, tuberculosis) before therapy should be considered.

Any noteworthy impact on liver or bone marrow function should give cause to dose reduction or transient or total discontinuation of treatment.

Combination with other treatments

Combination with TCS, TCI or narrow band UV phototherapy are established treatment combinations and considered safe. Concomitant us of ciclosporin is a relative contraindication. There is experience from rheumatoid arthritis for combining with the JAK inhibitor baricitinib.

Special considerations

MTX may be used for treatment of AE in both adults and children.

Subcutaneous administration increases bioavailability and tolerability, as well as adherence, compared to oral treatment.

MTX affects fertility and is teratogenic. Fertile women should use effective contraception. The same is recommended for men treated with MTX living with a woman of childbearing potential.

8.5. Mycophenolate mofetil

We **cannot make a recommendation** with respect to mycophenolate mofetil/ mycophenolic acid for the treatment of AE.	**0**	100%  (15/15) Expert Consensus

mycophenolate mofetil: off licence; commonly used dosage
adults: 1-3 g per day
children: 30-50 mg/kg per day

Mechanisms of action and efficacy

Mycophenolate mofetilis a prodrug of mycophenolic acid (MPA), an inhibitor of inosine-5'-monophosphate dehydrogenase. MPA depletes guanosine nucleotides preferentially in T and B lymphocytes and inhibits their proliferation. MPA also inhibits the glycosylation and expression of adhesion molecules, and the recruitment of lymphocytes and monocytes into sites of inflammation.[292]

A recent systematic review and meta-analysis[293] including 18 studies with a total of 140 adult and paediatric patients evaluated the efficacy of off-label use of MMF in patients with AE refractory or not tolerating other first line systemic agents. There was a significant reduction in pre to post SCORAD scores by 18 points (p = .0002) with 77.6% of patients reporting partial or full remission. Relapses occurred in 8.2% of cases. The average time for initial effects was 6.8 ± 7 weeks.

Dosage: acute flare, short term, long term

- off licence
- commonly used dosage
    - adults: 1-3 g per day
    - children: 30-50 mg/kg bodyweight per day
    - typically given in two divided doses
- We recommend combining MMF, as any systemic treatment, with emollients and, whenever needed, topical anti-inflammatory treatment in AE patients.

Safety

The most common side effect include headaches and gastrointestinal symptoms, followed by infections, especially during long-term therapy.

Haematological adverse effects include anemia, leukopenia, neutropenia and thrombocytopenia, albeit rarely.

Monitoring

- Complete blood count, renal and liver profile before therapy, then every 2 weeks for 1 month; monthly for 3 months; every 2-3 months thereafter;
- Screening for chronic infections (e.g. hepatitis B-/C, HIV) according to national and local guidelines
- Pregnancy testing before and during MMF therapy if indicated

Combination with other treatments

Concomitantly to MMF, topical therapy with corticosteroids and/or calcineurin inhibitors can be applied.

Special considerations

In case series, the efficacy and safety of MMF in children have been investigated. The drug has shown a positive treatment response with minimal adverse effects and appears to be better tolerated than AZA.[294]

9. Biologics

9.1. Dupilumab

We **recommend** dupilumab in AE patients who are candidates for systemic treatment.	↑↑	100%  (15/15) Evidence and consensus based, see Evidence Report

dupilumab: in licence for ≥ 6 years;
age 6-11: from 15kg <60kg, initially 300 mg s.c. day 1 and 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
adults: initially 600 mg s.c. day 1 followed by 300 mg Q2W

Certainty of evidence[2, 3]:

Short term (8-16 weeks) vs placebo (NMA medications used in clinical practice or likely to be approved soon)

⊕⊕⊕⊕ HIGH for mean difference/ standardized mean difference **EASI, change in signs, POEM, peak pruritus NRS, DLQI, QoL, itch**

⊕⊕⊕◯ MODERATE - ⊕⊕◯◯ LOW for undesirable effects

For dupilumab versus other drugs, see Evidence Report

Mechanisms of action and efficacy

Dupilumab is the first marketed fully human IgG4 monoclonal antibody (mAb) in the treatment of AE and has been available for treatment of adults for more than 2 years in many countries. Recently, it has also been approved for adolescents and children from6 years of age in some countries. Dupilumab binds to the α-subunit of the IL-4 receptor, which is part of both the IL-4 and IL-13 receptor complex. The safety and efficacy of dupilumab was primarily established in placebo-controlled studies in moderate-to-severe AE[181]. Dupilumab showed significant clinical effects across 3 distinct severity assessment tools: Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), and SCORing Atopic Dermatitis (SCORAD). Moreover, dupilumab treatment significantly reduced pruritus. Dupilumab has shown efficacy in both intrinsic and extrinsic AE.[295] Dupilumab is also registered for treatment of moderate-to-severe asthma, eosinophilic esophagitis, and chronic rhinosinusitis with nasal polyps, thereby covering several type 2 inflammatory diseases.

Dosage: acute flare, short term, long term

The approved dosing of dupilumab in adults consists of a 600 mg subcutaneous loading dose followed by maintenance doses of 300 mg every other week (Q2W). For children the following dosing regimens are used: 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.

Dupilumab has been used in an open label study for up to 3 years in adults with moderate-to-severe AE, but some former trial patients have continued open label on the medication much longer. Safety data were consistent with previously reported trials and the known dupilumab safety profile.[296]

Safety

Dupilumab treatment is in general well tolerated, and routine blood tests are not recommended, but a substantial number of patients develops conjunctivitis (over 30% in some 'real world' settings), of which most are mild-to-moderate.[297, 298] Topical treatment with anti-inflammatory eyedrops is often sufficient, without need to discontinue treatment.[299]

Monitoring

No biochemicals or instrumental exams are reported to be required for the monitoring of the therapy.

Combination with other treatments

An additional phase III trial, evaluated dupilumab treatment and a concomitant topicalcorticosteroid (TCS) compared with placebo and a concomitant TCS over 52 weeks.[300] The co-primary end points included IGA score of 0 or 1 and EASI-75, were assessed at week 16: more patients who received dupilumab plus topical corticosteroids achieved the co-primary endpoints of IGA 0/1 and EASI 75. Results at 52 weeks were similar. Approximately 15% more subjects achieved a 75% reduction in the EASI score at week 16 in this trial compared with previous phase III studies where dupilumab was administered as monotherapy.[181]

Combination therapy with TCS, TCI, and UV light treatment is well established.

Special considerations

AE patients with type 2 comorbidities like asthma, allergic rhinoconjunctivitis with nasal polyps, and/or eosinophil esophagitis may also have benificial effects of dupilumab treatment on these diseases.

9.2. Lebrikizumab

Lebrikizumab is currenty not licensed for any indication worldwide. Therefore we do not give a specific recommendation for the use in AE.

Mechanisms of action and efficacy

Lebrikizumab is a high-affinity humanized immunoglobulin G4 mAb that binds specifically to soluble interleukin 13 and selectively prevents formation of the IL-13Rα1/IL-4Rα heterodimer receptor signaling complex. In a randomized, placebo-controlled, double-blind, phase IIb study, adults with moderate-to-severe AE patients were randomized to placebo every 2 weeks or to subcutaneous injections of lebrikizumab at the following doses: 125 mg every 4 weeks (250 mg loading dose [LD]), 250 mg every 4 weeks (500-mg LD), or 250 mg every 2 weeks (500 mg LD at baseline and week 2).[301]

Compared with placebo lebrikizumab groups showed dose-dependent, statistically significant improvement in EASI scores, pruritus NRS score, POEM and IGA.[301]

Dosage: acute flare, short term, long term

Although all the different dosages of lebrikizumab proved to be effective, optimal dosing regimens have yet to be determined. Phase 3 studies are currently underway testing lebrikizumab 250mg Q2Win the induction phase, and both 250mg Q2W and Q4W in the maintenance phase.

Safety

Treatment-emergent adverse events were reported in 24 of 52 placebo patients (46.2%) and in lebrikizumab patients as follows: 42 of 73 (57.5%) for 125 mg every 4 weeks, 39 of 80 (48.8%) for 250 mg every 4 weeks, and 46 of 75 (61.3%) for 250 mg every 2 weeks; most were mild-to-moderate and did not lead to discontinuation. In all lebrikizumab groups, herpes virus infections and conjunctivitis were reported at low rates.

Simpson et al. reported injection site reactions (1.3%), herpes infection (3.8%), eosinophilia (3.2%) with no associated clinical symptoms, and conjunctivitis (9.6%) as adverse events in patients treated with lebrikizumab.[302]

Notably, lebrikizumab appears to have lower rates of ocular complications than dupilumab.

Monitoring

No biochemical or instrumental exams are reported to be required for the monitoring of the therapy.

Combination with other treatments

The use of topical corticosteroids during the flares of AE could be useful in combination with lebrikizumab, and is under investigation in the phase 3 program.

9.3. Nemolizumab

Nemolizumab is currenty not licensed for any indication worldwide. Therefore, we do not give a specific recommendation for the use in AE.

Mechanisms of action and efficacy

Nemolizumab is a humanized mAb targeting the IL-31 receptor alpha chain (IL-31RA), which was initially developed for the treatment of AE-related pruritus.

In a phase II, randomized, double-blind, placebo-controlled, 12-week trial, nemolizumab at monthly doses significantly improved pruritus.[303]

In a 2b study with nemolizumab 30mg dosing and TCS, there were significant improvements in signs and symptoms of AD - EASI scores, PP-NRS, sleep and DLQI score, which was confirmed in a post-hoc sub-analysis of the EASI ≥ 16 cohort. [304, 305]

In a recently published 16-week, double-blind, phase III trial, Japanese patients with AE and moderate-to-severe pruritus received subcutaneous nemolizumab (60 mg) or placebo every 4 weeks until week 16, with concomitant topical agents.[306] The primary end point was the mean percent change in the visual-analogue scale (VAS) score for pruritus from baseline to week 16. Secondary end points included the time course of change in the VAS score for pruritus up to week 4, EASI score, DLQI, Insomnia Severity Index, and safety. At week 16, the mean percent change in the VAS score was -42.8% in the nemolizumab group and -21.4% in the placebo group. The use of subcutaneous nemolizumab in addition to topical agents for atopic dermatitis resulted in a highly significant reduction in pruritus than placebo plus topical agents.

Dosage: acute flare, short term, long term

The first phase II study investigating nemolizumab published in 2017 investigated 0.1 mg/kg, 0.5 mg/kg, 2 mg/kg dosages administered every 4 weeks and 2 mg/kg dosage administered every 8 weeks. Results at 12 weeks found a significant, dose-dependent improvement in the primary outcome of pruritus for all groups that received nemolizumab every 4 weeks, as compared with placebo.[303] In a two-part, phase II, randomized control trial published in 2018, Kabashima et al.[306] compared three different nemolizumab dosages: 0.1 mg/kg, 0.5 mg/kg, 2 mg/kg adminstered every 4 weeks and 2 mg/kg administered every 8 weeks. All the parameters considered in the study showed an improvement and no evidence was found that the highest dosage was more effective than the lowest. Furthermore, the study showed that the positive outcomes obtained with Nemolizumab were maintained for up to 64 weeks.

In another 24-week, randomized, double-blind, multicenter study published in 2019 by Silverberg et al.[304], three different nemolizumab dosages, 10 mg, 30 mg and 90 mg, were compared in an ethnically more diverse population. The drug was administered once every 4 weeks and nemolizumab 30 mg showed maximum dosage efficacy in improving EASI, IGA, and pruritus.

In the latest published study conducted in Japanese patients,[306] the dosage tested was 60mg, administered every 4 weeks. At the reported dosage, nemolizumab showed a greater efficacy in reducing pruritus, compared to placebo plus topicals.

Safety

The most frequent adverse events related to the drug are reported to be injection-related reactions, musculoskeletal and connective tissue symptoms, upper respiratory tract infections, nasopharyngitis, peripheral oedema, and increased creatine phosphokinase.[304]

The authors conclude that longer and larger trials are necessary to determine whether nemolizumab has a durable effect and is safe for AE patients.[304]

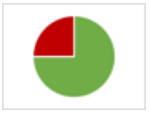
Monitoring

No biochemical or instrumental exams are reported to be required for the monitoring of the therapy.

Combination with other treatments

According to the available study trials, the use of topical treatments such as emollients, corticosteroids and calcineurin inhibitors as a rescue therapy, in addition to nemolizumab, could have a synergistic effect in the treatment of AE and AE-related pruritus.

9.4. Omalizumab

We **cannot make a recommendation** with respect to the use of omalizumab for the treatment of AE.	**0**	>75%  (13/15) Expert Consensus

Omalizumab: in label for allergic asthma (≥ 6 years), chronic rhinosinusitis with nasal polyps (CRSwNP) (≥ 18 years) and chronic spontaneous urticaria (≥ 12 years)
Commonly used dosage:
Dosage (allergic asthma and CRSwNP): depends on baseline IgE (IU/ml), measured before the start of treatment, and body weight. The maximum recommended dose is 600 mg omalizumab every two weeks. Please refer to the SmPC for further details. Dosage (chronic spontaneous urticaria): 300 mg every four weeks.

Mechanisms of action and efficacy

Most AE patients have elevated serum IgE levels, but the pathogenic role of IgE in AE remains unknown. The anti-IgE antibody omalizumab has been used with great success for treatment of chronic spontaneous urticaria (CSU). A recent systematic review and meta-analysis has assessed the preclinical and trial data regarding omalizumab treatment of AE, which are conflicting.[307]

Omalizumab is licensed for treatment of asthma and CSU, but not for treatment for AE.

Omalizumab is binding free IgE, which leads to immune complexes of IgE and omalizumab. IgE bound to omalizumab cannot bind to the alpha chain of the high affinity receptor for IgE, thereby inhibiting its binding to mast cells, basophils and epidermal dendritic cells[308, 309], and subsequent immunological effects.

There are many case reports and case series,[307] but only few controlled trials studying omalizumab treatment of AE.[307, 310] In summary, the data show a measurable, but moderate efficacy of omalizumab for improving signs and symptoms of AE.[307, 311] There is no predictive marker linked to a better clinical response, and most of the published evidence is of low quality. The safety of omalizumab is very good[307], but the unpredictable and statistically low efficacy prevents a general recommendation for omalizumab regarding treatment of AE.

Dosage: acute flare, short term, long term

Adult:

Diffent dosages have been tested in AE patients, ranging from 150–450 mg every 2 weeks or every 4 weeks. A recent systematic review and meta-analysis by Wollenberg et al. found that patients with lower baseline IgE showed a positive response to treatment with omalizumab compared with patients with very high-to-extremely high serum IgE.[307]

An older systematic review and meta analysis by Wang et al. also found that IgE serum concentrations of lower than 700 IU/mL were associated with a better clinical response, compared with IgE concentrations of 700 to >5000 IU/mL. Age, sex, baseline clinical disease severity, the history of concomitant asthma, and the use of 600 mg/month or more of omalizumab showed no significant association with the clinical results associated with omalizumab use.[312]

Children:

The ADAPT (Atopic Dermatitis Anti-IgE Paediatric Trial) trial evaluated the possible role of omalizumab in the management of severe paediatric AE with concomitant allergic disease (asthma, allergic rhinoconjuncitivitis or food allergies) for 24 weeks. The drug dose was determined by baseline total IgE (range: 30 to 1500 IU/ml), measured before the start of treatment, and body weight (kg) and calculated using the formula: 0.016 x weight (kg) x total IgE level (kU/l) in 2-4 weekly injections. The study showed that omalizumab significantly reduced disease severity and improve QoL in paediatric patients with severe AE and highly elevated IgE levels (median baseline total IgE of 8373 IU/L) compared with placebo.[310] However, this improvement was below the minimal clinically important difference for the main outcome (objective SCORAD).

Safety

There is a general consensus about the overall good safety profile of omalizumab with some controlled studies reporting excellent tolerability up to 4 years. A 2009 revision of data from controlled trials concluded that incidence of anaphylaxis was 0.14% in omalizumab-treated patients and 0.07% in control subjects. Of note, no serum-sickness attributable to the drug and no anti-omalizumab antibodies have been reported to date.[313]

There are no reported interactions of omalizumab with other medications used for AE or other allergic diseases. If clinically needed, omalizumab may be considered during pregnancy. More attention has been put over the appearance of gut parasite infections in treated patients, since IgE is an important player in the host defence against parasitic helminths. A randomized placebo-controlled trial in 137 adult subjects with respiratory allergy at high risk of helminth infection showed a modest increase of the incidence of parasitism in the active group.[314]

Monitoring

No biochemicals or instrumental exams are reported to be required for the monitoring of the therapy. IgE levels increase following administration of omalizumab and may remain elevated for up to 1 year following discontinuation of the drug.

9.5. Tralokinumab

We **recommend** tralokinumab in AE patients who are candidates for systemic treatment.	↑↑	100%  (15/15) Evidence and consensus based, see Evidence Report

tralokinumab: in licence for ≥ 12 years;
age 12-17: initially 600 mg s.c. day 1 followed by 300 mg Q2W
adults: initially 600 mg s.c. day 1 followed by 300 mg Q2W
At prescriber's discretion, every fourth week dosing may be considered for patients who achieve clear or almost clear skin after 16 weeks of treatment.

Certainty of evidence[2, 3]:

Short term (8-16 weeks) vs placebo (NMA medications used in clinical practice or likely to be approved soon)

⊕⊕⊕⊕ HIGH for mean difference/ standardized mean difference **EASI, change in signs, POEM, peak pruritus NRS, DLQI, QoL, itch**

⊕⊕◯◯ LOW for undesirable effects

Mechanisms of action and efficacy

Tralokinumab is a fully human, high affinity IgG4 mAb, which neutralizes IL-13, and has been approved by the EMA in summer 2021.[315] In two 52-week, double-blind, placebo-controlled, phase III trials, adults with moderate-to-severe AE were randomized to subcutaneous tralokinumab 300 mg every 2 weeks or placebo.[185] Tralokinumab monotherapy was superior to placebo at 16 weeks of treatment. Co-primary endpoints were IGA score of 0 or 1 and EASI 75 at week 16. Patient achieving an IGA score of 0/1 and/or EASI 75 with tralokinumab at week 16 were re-randomized to tralokinumab Q2W or every 4 weeks or placebo for 36 weeks. The majority of week 16 tralokinumab-responders maintained response at week 52 with continued tralokinumab treatment without any rescue medication. In a randomised, double-blind, phase IIII trial 301 adolescent patients received either 300 mg or 150 mg of tralokinumab or placebo. After 16 weeks, significantly more patients in the tralokinumab arms showed an EASI 75 response (27.8%, 28.6%, 6.4%) or an IGA of 0 or 1 (17.5%, 21.4%, 4.3%). Subjects achieving a clinical response (IGA = 0, 1; or EASI75) at week 16 without use of rescue medication were re-randomized to maintenance dosing regimens. At 52 weeks, EASI-75 response ranged from 44.4% to 63.3% in the different maintenance dosing regimens.[316]

Dosage: acute flare, short term, long term

The recommended dosage is 300 mg every 2 weeks after a loading dose of 600 mg at treatment onset. At prescriber's discretion, every fourth week dosing may be considered for patients who achieve clear or almost clear skin after 16 weeks of treatment.

Phase III trials have also investigated what happens when patients who do well for 16 weeks on tralokinumab continue treatment as labeled, reduce treatment frequency, or discontinue treatment.

After 16 weeks, patients who reached EASI 75 or IGA success were re-randomized to continue treatment every two weeks, titrate down to every four weeks, or use placebo. At 52 weeks, without TCS, more than 55% of patients who continued twice-monthly treatment maintained EASI 75, as did approximately 50% of patients treated monthly. More than 51% of patients who stayed on twice-monthly dosing maintained IGA 0 or 1, versus 39% and 45% of patients who switched to monthly dosing.

Safety

In the two studies, adverse events were reported in 76.4% and 61.5% of patients receiving tralokinumab and in 77.0% and 66.0% of patients receiving placebo in the 16-week initial period.

Notably, tralokinumab appears to have lower rates of ocular complications than dupilumab.[185]

The combination therapy with TCS, TCI and UV light treatment is possible.

Monitoring

No biochemical or instrumental exams are reported to be required for the monitoring of the therapy.

Combination with other treatments

In an additional phase III double-blind, placebo study the efficacy and safety of tralokinumab in combination with TCS as needed in patients with moderate-to-severe AE were evaluated. At week 16, significantly more tralokinumab-treated patients than placebo achieved IGA 0/1 and EASI 75. Nine out of ten EASI 75 responders at week 16 maintained response at week 32 with continued tralokinumab and TCS as needed.[317]

10. JAK-Inhibitors

The janus kinase (JAK) family, constituting JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), are a class of cytoplasmic tyrosine kinases.[318] JAKs dock to the intracellular part of cytokine receptor chains to generate functional signaling complexes and regulate the inflammatory process through activating the intracytoplasmic transcription factors termed as signal transducer and activator of transcription (STAT). When activated, STAT proteins produce dimers, which translocate into the nucleus and either positively or negatively regulate downstream target gene expression of inflammatory mediators, suggesting that inhibiting JAK activity may be more effective than targeting a single cytokine. Past the disruption of cutaneous inflammatory cytokine signaling, JAK inhibition has been reported to attenuate chronic itch and improve skin barrier function by regulating the expression of skin barrier protein filaggrin.[319, 320]

10.1. Abrocitinib

We **recommend** abrocitinib in AE patients, who are candidates for systemic treatment.	↑↑	100%  (15/15) Evidence and consensus based see, Evidence Report

abrocitinib: in licence for adults;
dosage adults: 200 mg per day, reduction to 100 mg per day possible, depending on treatment response
dosage adults age ≥ 65: 100 mg per day

Certainty of evidence[2, 3]:

Short term (8-16 weeks) vs placebo (NMA medications used in clinical practice or likely to be approved soon)

⊕⊕⊕⊕ HIGH for mean difference/ standardized mean difference **EASI, change in signs, POEM, peak pruritus NRS, DLQI, QoL, itch**

⊕⊕◯◯ LOW - ⊕◯◯◯ VERY LOW for undesirable effects

The EMA Committee for Medicinal Products for Human Use adopted a positive opinion on 14th October 2021 for adults. In the UK, abrocitinib is currently licensed for AE in those aged 12 and above.

Mechanisms of action and efficacy

Abrocitinib is an oral JAK1 selective inhibitor and has shown efficacy in patients with moderate-to-severe AE when used as a monotherapy (MONO-1 and -2 studies) and in combination with topical therapies in achieving treatment response in comparison to placebo (COMPARE study), as measured using IGA and EASI-75 response. For instance, the proportion of patients with EASI-75 response at week 12 was significantly higher with abrocitinib 100 mg (~40-45%) and abrocitinib 200 mg (~61-63%) compared to placebo (~10-12%) in the MONO studies. In the COMPARE study the proportion of patients with EASI-75 response was significantly higher with abrocitinib 100 mg (~59%) and abrocitinib 200 mg (~70%) compared to placebo (27%)).[259] Similar efficacy has been demonstrated in the adolescent JADE

TEEN trial for both the 100mg and 200mg doses, in combination with topical therapies.[321] Importantly, in the COMPARE study (which had dupilumab as a comparator arm) higher responder rates were observed with abrocitinib 200 mg compared to dupilumab (p-values not calculated) after 16 weeks of treatment. The efficacy of abrocitinib 100 mg and dupilumab was similar in this subgroup. The results indicate that abrocitinib 200 mg may provide a higher probability of treatment response compared to dupilumab in patients with severe AE.[322]

Dosage: acute flare, short term, long term

Abrocitinib is licenced at the 100mg and the 200mg daily doses, with the lower dose recommended for adolscents as a starting dose. One study assessed risk and probability of flares and recapture of treatment response following a flare. Of 1233 patients, 798 responders to induction with abrocitinib 200 mg (64.7%) were randomly assigned to dose maintenance, dose reduction or treatment withdrawal (placebo). The flare probability during maintenance was 18.9%, 42.6%, and 80.9% with abrocitinib 200 mg, abrocitinib 100 mg, and placebo, respectively by week 52. Among patients with flare in the abrocitinib 200 mg, abrocitinib 100 mg, and placebo groups, 36.6%, 58.8%, and 81.6% regained IGA 0/1 response, respectively, and 55.0%, 74.5%, and 91.8% regained EASI index response, respectively, with rescue treatment of abrocitinib 200 mg plus medicated topical therapy.[323]

Safety

Based on long-term follow up of patients from the phase II and III trials as well as one long-term extension study, with a total n of 2856 (1614 patient-years (PY); total exposure in the all-abrocitinib cohort was ≥ 24 weeks in 1248 patients and ≥ 48 weeks in 606 (maximum 108 weeks). In the placebo-controlled cohort (n = 1540), dose-related adverse events (200 mg, 100 mg, placebo) were nausea (14.6%, 6.1%, 2.0%), headache (7.8%, 5.9%, 3.5%), and acne (4.7%, 1.6%, 0%). Platelet count was reduced transiently in a dose-dependent manner; 2/2718 patients (200-mg group) had confirmed platelet counts of $< 50 \times 10^3/mm^3$ at week 4. Incidence rates (IRs) were 2.33/100PY and 2.65/100 PY for serious infection, 4.34/100PY and 2.04/100PY for herpes zoster, and 11.83/100PY and 8.73/100PY for herpes simplex in the 200-mg and 100-mg groups, respectively.[324]

Monitoring

For baseline screening, the manufacturer's UK label laboratory monitoring recommendations are full blood count including platelet count, absolute lymphocyte count (ALC), absolute neutrophil count (ANC), and haemoglobin (Hb) as well as lipid parameters. A chest radiograph, creatinine phosphokinase level and an infection screening for HIV, hepatitis B and C as well as TB is advisable before initiation of therapy.

In practice, we recommend the same baseline screening and treatment monitoring investigations for all JAK inhibitors. For baseline screening this is a full blood count, renal, liver and lipid profile as well as creatinine phosphokinase levels and hepatitis and TB screen, including a chest radiograph.

For monitoring purposes, we recommend a full blood count, renal, liver and lipid profile as well as creatinine phosphokinase level at four weeks into treatment and then three-monthly while on therapy.

Combination with other treatments

No studies assessing the use of abrocitinib with other systemic therapies have been published to date.

Special considerations

Abrocitinib is a new JAK inhibitor and has not been formally tested in other inflammatory diseases.

10.2. Baricitinib

We **recommend** baricitinib in AE patients, who are candidates for systemic treatment.	↑↑	100%  (15/15) Evidence and consensus based, see Evidence Report

baricitinib: in licence for adults;
dosage adults: 4 mg per day, reduction to 2 mg per day possible, depending on treatment response

Certainty of evidence[2, 3]:

Short term (8-16 weeks) vs placebo (NMA medications used in clinical practice or likely to be approved soon)

⊕⊕⊕⊕ HIGH for mean difference/ standardized mean difference **EASI, change in signs, POEM, peak pruritus NRS, DLQI, QoL, itch**

⊕⊕◯◯ LOW - ⊕◯◯◯ VERY LOW for undesirable effects

Mechanisms of action and efficacy

Baricitinib is an oral selective JAK1 and JAK2 inhibitor. The drug has been tested in one phase 2 and several phase 3 trials in adults with moderate-to-severe AE at 1mg, 2mg and 4mg once daily against placebo, showing significant improvement with regard to EASI from baseline to 16 weeks, in particular in the two higher doses (2 mg daily (mean difference, 5.6-point reduction; 95% CI, 0.4-10.9 [GRADE assessment: moderate certainty]) and 4 mg daily (mean difference, 5.2-point reduction; 95% CI, 0.1-10.4 [GRADE assessment: moderate certainty]).[259] Similar efficacy has been shown in these studies with regard to the IGA and itch scores. The concomitant use of topical corticosteroids was allowed in one trial.[325]

Dosage: acute flare, short term, long term

At present, Baricitinib data is available up to 52 weeks follow up[326], demonstrating sustained efficacy. There is no study that has looked at acute flare treatment and the paediatric study programme is still underway[327] and no clear dosing guidance for paediatric patients is currently available.

Safety

The most common side effects with baricitinib in clinical trials include an increase in LDL cholesterol, upper respiratory tract infections, and headache. Acne is less common than with other JAK inhibitors. Infections reported with baricitinib include herpes simplex. However, the rate of these events reported in a recent combined safety study including 2531 patients from 8 RCTs who were given baricitinib for 2247 patient-years (median duration 310 days) was overall low: eczema herpeticum (n = 11), cellulitis (n = 6) and pneumonia (n = 3). There were four opportunistic infections reported.[328] A transient increase of CPK may be seen, especially after extensive bodily exercise. No malignancies, gastrointestinal perforations, positively adjudicated cardiovascular events or tuberculosis were reported in the placebo-controlled period in baricitinib-treated patients. The frequency of herpes simplex was higher in the 4 mg

group (6.1%) compared to the 2 mg (3.6%) and placebo groups (2.7%). Long-term safety data beyond 16 weeks is available from an integrated data base covering mostly rheumatoid arthritis patients for up to 9.3 years of treatment.[329]

Monitoring

For baseline screening, the manufacturer advises that patients with suspected hepatitis B consult a liver specialist for advice before initiation of treatment. Lipid and liver profiles need to be regularly monitored following treatment initiation. Screening for any haematological abnormalities is also advised.

In practice, we recommend the same baseline screening and treatment monitoring investigations for all JAK inhibitors. For baseline screening this is a full blood count, renal, liver and lipid profile as well as creatinine phosphokinase levels and hepatitis and TB screen, including a chest radiograph.

For monitoring purposes, we recommend a full blood count, renal, liver and lipid profile as well as creatinine phosphokinase level at four weeks into treatment and then three-monthly while on therapy.

Combination with other treatments

No studies assessing the use of baricitinib with other systemic therapies in AE patients have been published to date, but the combination therapy with MTX is an established combination regimen in the management of rheumatoid arthritis.[330]

Special considerations

AE patients with concomitant inflammatory diseases, such as rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis are likely to experience benificial effects. Baricitinib is already licensed for this indication.

10.3. Upadacitinib

We **recommend** upadacitinib in AE patients who are candidates for systemic treatment.	↑↑	100%  (15/15) Evidence and consensus based, see Evidence Report

upadacitinib: in licence for ≥ 12 years;
adults: 15 or 30 mg per day; age ≥ 65: 15 mg per day
age 12-17 (>= 30 kg bw): 15 mg per day

Certainty of evidence[2, 3]:

Short term (8-16 weeks) vs placebo (NMA medications used in clinical practice or likely to be approved soon)

⊕⊕⊕⊕ HIGH for mean difference/ standardized mean difference **EASI, change in signs, POEM, peak pruritus NRS, itch**

⊕⊕⊕◯ MODERATE - ⊕⊕◯◯ LOW for undesirable effects

Upadacitinib is licensed for AE in adolescents (12 years and above) and adults.

Mechanisms of action and efficacy

Upadacitinib is a selective and reversible Janus Kinase (JAK) inhibitor. There is one phase 2 trial including 167 adult patients that investigated three different doses of upadacitinib (30 mg/d, 15 mg/d and 7.5 mg/d) for AE compared to placebo.[331] The trial was conducted over 16 weeks. Upadacitinib was superior to placebo for all dosage groups in EASI (mean change (SE) 74% (6.1%) for 30mg, 62% (6.1%) for 15mg, 39% (6.2%) for 7.5 mg and 23% (6.4%) for placebo (p=0.03, <0.001, <0.001). There were also significant improvements seen with regard to the SCORAD index, NRS pruritus, and POEM scores. The trials published since have shown similar efficacy.[186, 188, 332]

In a direct head-to-head trial enrolling adult AE patients randomized to receive upadacitinib (n=348) and dupilumab (n=344) 247 patients receiving upadacitinib (71.0%) and 210 patients receiving dupilumab (61.1%) achieved EASI-75 at 16 weeks (*P* = .006). All ranked secondary end points also demonstrated the superiority of upadacitinib vs dupilumab, including improvement in Worst Pruritus NRS as early as week 1, achievement of EASI-75 as early as week 2, and EASI-100 at week 16. Rates of serious infection, eczema herpeticum, herpes zoster, and laboratory-related adverse events were higher for patients who received upadacitinib, whereas rates of conjunctivitis and injection-site reactions were higher for patients who received dupilumab.

Dosage: acute flare, short term, long term

Upadacitinib is licensed at the 15mg and 30mg doses for AE, and at 15mg for rheumatoid arthritis, psoriatic arthritis and ankylosing spondilitis. Follow up until week 52 is now available, showing long-term efficacy and safety profiles similar to the 16 week trials.[333] There is no study that has looked at acute flare treatment, and there are currently early phase AE trials in children >6 months.

Safety

The cumulative incidence rates of adverse events were 78.6% for 30 mg, 76.2% for 15 mg, 73.8% for 7.5 mg and 62.5% for placebo in the phase 2 trial and have been similar in the studies reported since.[331] Upper respiratory tract infections and acne were the most frequently reported adverse events for upadacitinib. The cumulative incidence rates of severe adverse events were 0% for 30mg, 2.4% for 15mg, 4.8% for 7.5mg and 2.4% for placebo. Low withdrawal rates were reported in the placebo and upadacitinib groups (n<5 for each group). In a phase 3 trial, 272 Japanese patients (age: 12-75 years) with moderate-to-severe AE were randomized in a 1:1:1 ratio to receive 15 mg upadacitinib, 30 mg upadacitinib or placebo (each in combination with a TCS) to evaluate the safety of upadacitinib in combination with TCS. Treatment-emergent adverse event (TEAEs) were reported for 56.0%, 63.7% and 42.2% of participants, respectively at week 24. The most frequently reported TEAEs were acne (13.2%, 19.8%, 5.6%), nasopharyngitis (13.2%, 15.4%, 15.6%), and herpes zoster infection (0%, 4.4%, 0%). No thromboembolic events, malignancies, gastrointestinal perforations or deaths occurred.[334]

Monitoring

The manufacturer advises that patients are screened for viral hepatitis B and C and TB. Lipid and liver profiles need to be measured at baseline and regularly following treatment initiation. Screening and monitoring for any haematological abnormalities is also advised, no later than 12 weeks.

In practice, we recommend the same baseline screening and treatment monitoring investigations for all JAK inhibitors. For baseline screening this is a full blood count, renal, liver and lipid profile as well as creatinine phosphokinase levels and hepatitis and TB screen, including a chest radiograph.

For monitoring purposes, we recommend a full blood count, renal, liver and lipid profile as well as creatinine phosphokinase level at four weeks into treatment and then three-monthly while on therapy.

Combination with other treatments

No studies assessing the use of upadacitinib with other systemic therapies in AE patients have been published to date, but the combination therapy with MTX is an established combination regimen in the management of rheumatoid arthritis, albeit only with the 15mg once a day dose.[335]

Special considerations

AE patients with concomitant inflammatory diseases, such as rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis are likely to experience benificial effects, as upadacitinib is already licensed for this indication.[336]

11. Other systemic treatment

11.1. Alitretinoin

We **suggest** alitretinoin for AE patients with severe chronic *hand eczema*, who are candidates for systemic treatment, duely considering its teratogenicity.	↑	100%  (15/15) Expert Consensus

alitretinoin: in label for adults with severe chronic hand eczema unresponsive to topical corticosteroids; dosage adults 10 - 30 mg per day

Mechanisms of action and efficacy

Alitretinoin is a retinoid binding both retinoic acid (RAR) and retinoic X (RXR) receptors, thus delivering anti-inflammatory and anti-proliferative effects. It is licensed in some European countries for the treatment of chronic hand eczema irrespectively of its pathogenesis.

There is one large, multicenter randomized, placebo controlled clinical trial involving 1032 patients with chronic hand eczema, about one third of which were probably atopic hand eczema patients.[337] Improvement of eczema was seen in 75% of the patients. The patient group suffering from atopic hand eczema was notanalyzed separately, and extrapalmar symptoms have not been assessed in this trial.

Six patients with AE and prominent hand involvement were treated with alitretinoin for twelve weeks in an uncontrolled, open label trial.[338] Both, palmar and extrapalmar lesions improved during the trial, as shown by the modified Total Lesion Symptom Score (mTLSS) hand eczema score and the SCORAD.

Dosage: acute flare, short term, long term

According to the mode of action, alitretinoin is suitable for long-term treatment. An alitretinoin treatment course should be planned for 3 to 6 months.

The dosage of alitretinoin is 10-30 mg per day.

Safety

As alitretinoin is highly teratogenic, all females of childbearing potential must adhere to a strict birth control programme.

Monitoring

Before and during therapy: liver enzymes (aspartate aminotransferase (ASAT), aspartate aminotransferase (ALAT), gamma-glutamyl transpeptidase (GGT)), cholesterol, triglycerides, basal thyroid stimulating hormone (TSH), free thyroxine (fT4) peripheral blood levels; pregnancy test in women with childbearing potential.

Combination with other treatments

Concomitantly to alitretinoin, topical therapy with corticosteroids, calcineurininhibitors and emollients can be applied.

Special considerations

A retrospective analysis of children treated with alitretinoin because of hand eczema and other diagnoses including two severe AE patients, revealed that the response to alitretinoin was moderate in one subject, whereas the other patient failed to improve even after extending treatment to up to 11 months.[339]

11.2. H4R-blocking antihistamines

Mechanisms of action and efficacy

Histamine 4 receptor (H4R)-blocking antihistamines have been recently investigated for moderate and severe AE. In a phase 2a RCT, an investigational compound (JNJ-39758979) showed some efficacy but the study was interrupted after 6 weeks because of safety reasons (severe neutropenia).[340]

In a RCT with another investigational compound (ZPL-3893787) reductions in EASI score and SCORAD score were 50% and 41% respectively vs 27% and 26% for placebo, after 8 weeks. Improvement of pruritus was not different from placebo without relevant safety findings.[341] The clinical development of this substance was stopped after negative results on efficacy after interim analysis of a phase 2b with a high placebo response of 50% (clinicaltrials.gov).

There is limited evidence available to support the general use of H4R antihistamines for the treatment of AE lesions and pruritus.

11.3. Therapies that were used in past

Immunoadsorption

Immunoadsorption (IA) has been used in patients with AE and elevated total IgE levels based on the assumption that a reduction in IgE might result in disease improvement. Immunoadsorption was reviewed in the previous AE guidelines, but is expected to be scarcely used in the future, as multiple newer effective and safe treatments are available.

Mast cell stabilizers

Mast cell stabilizers block mast cell degranulation preventing the release of histamine and related mediators. Mast cell stabilizers were reviewed in the previous AE guidelines, but they are expected to be scarcely used in the future, as multiple newer effective and safe treatments are available.

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) provides immunomodulatory therapy in inflammatory and autoimmune diseases. IVIG was reviewed in the previous AE guidelines, but is expected to be scarcely used in the future, as multiple newer effective and safe treatments are available.

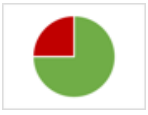
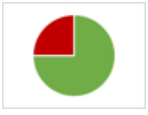
Leukotriene antagonists

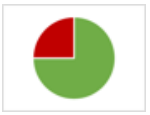
Montelukast is a cysteinyl leukotriene receptor antagonist that blocks the action of LTD4, LTC4 and LTE4. Montelucast was reviewed in the previous AE guidelines but is expected to be scarcely used in the future, as multiple newer effective and safe treatments are available.

Apremilast

Apremilast is a small molecule phosphodiesterase (PDE) 4 inhibitor that has been approved for the treatment of psoriasis arthritis and moderate-to-severe plaques psoriasis. Apremilast was reviewed in the previous AE guidelines but is expected to be scarcely used in the future, as multiple newer effective and safe treatments are available. The apremilast clinical program in the treatment of AE has been discontinued.

12. Avoidance techniques in atopic eczema

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

We **recommend** the avoidance of tobacco smoke for the prevention of AE.	↑↑	>75%  (17/18) Expert Consensus

Pollen avoidance

Pollen-related flares can be observed in sensitized atopic patients. Exacerbation of AE may occur after either direct skin contact or inhalation of pollen allergens.[342] Whether pollen avoidance leads to the prevention of flares in AE, has formally not been shown yet.

A reduced concentration of pollen indoors may help to prevent flares in patients highly sensitized to pollen. Keeping windows closed during high pollen peaks or the restrictions of outdoor activities in high pollen containing areas (e.g. lawn mowing) may be helpful. Frequently ventilated indoor spaces in rainy weather or at night/early morning, as well as the use of special pollen filters in air conditioners may also be advised. Skin contact with pollen-vectorized clothes or pets should be avoided. High-altitude climate may be recommended due to its lower pollen count compared to average living areas.[36, 65] These measures may however be difficult to maintain.[65]

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.[343-345] Measures of reducing exposure include mattress encasing, the use of adequate indoor ventilation (filter, well-aeration), and the avoidance of wall washing on high temperature.[65] HDM, a common indoor allergen occurring in dust, may be reduced by cleaning regularly. Complete eradication by e.g. encasing is not possible.

Animal dander avoidance

When allergies to furry animals are evident, their avoidance is recommended.[65] Particularly the exposure to cat allergens may be a risk factor for the development of inflammatory skin lesions as well as respiratory symptoms in sensitized patients with AE.[346] There may be an exception for dogs due to a suggested general protective effect of dog-keeping in the development of AE.[347]

Exercise/perspiration/physical activity

In AE patients heat and excessive sweating is one of the main factors reported to exacerbate itch.[348] 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.[349, 350] 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.[348] 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 for use and which to avoid. Clothing-related exacerbation can be subjective.[351] There is no evidence from high quality studies that certain fabrics improve the severity of AE.[351, 352] 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.[353, 354] It is difficult to investigate whether the psychological stress is a cause or consequence of the AE exacerbation, and in many case it is probably both. There is a positive correlation between maternal stress and offspring AE.[355, 356] Although evidence from larger studies is lacking, patients report that stress induces itch and flaring of the disease.[357, 358] (see chapter psychological intervention)

Pollution

In a systematic review of environmental epidemiologic studies about air pollution and AE acceptable evidence was found that, based on small-scale exposure measurements (so-called PM 2.5., i.e. particles with less than 2.5 µm diameter) , especially truck traffic emissions increased AE prevalence. PM 2.5 are primarily comprised of organic carbon compounds, nitrates, and sulfates. For large-scale exposures to larger particles (PM10) or SO2 the review did not find an effect on AE prevalence.[359, 360] Additional environmental risk factors for AE identified in single studies[361] were carbon monoxide (CO) exposure during first trimester, CO exposure within past 12 months to CO level > 1 ppm above annual CO, high total volatile organic compounds (TVOC) in infant's bedrooms at 6 months and AE at 36 months, and nitric oxide (NO2); the latter found as risk factor for AE in four different studies. So far the role of pollutants as trigger factor of pre-existing AE has not properly been described.

Tobacco smoke

The association of AE with active smoking was found to be significant in a metaanalysis (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 adults.[362] The results of a recent registry study of 908 patients with AE 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 (o-SCORAD and EASI scores) did not differ between smokers and non-smokers in this study. [363]

13. Dietary interventions in atopic eczema

We **recommend** to identify individual dietary trigger factors in patients with AE, to avoid these in the future, with the aim of prolonging remission or clearance.	↑↑	>75%  (16/17) Expert Consensus

<u>IgE-mediated food allergy (immediate reactions):</u> We **recommend** diagnostic procedures for the elucidation of IgE-mediated food allergy (food specific IgE and/or SPT, diagnostic elimination diets and challenge tests) in AE patients with a history of *food-induced immediate symptoms*.	↑↑	
<u>IgE-mediated food allergy (immediate reactions) plus food-induced AE "delayed hypersensitivity":</u> We **recommend** diagnostic procedures for the elucidation of combined reactions to foods (immediate reactions plus food-induced eczema (food specific IgE and/or SPT, diagnostic elimination diets and challenge tests)) in AE patients with a history of *food-induced symptoms, including worsening of AE*.	↑↑	>75%  (16/18)[1] Expert Consensus
<u>History or suspicion of food-triggered AE "delayed hypersensitivity":</u> We **suggest** diagnostic procedures for the elucidation of food as a trigger factor of AE (food specific IgE and/or SPT, diagnostic elimination diets and challenge tests) in patients with moderate-to-severe AE and with a *history or suspicion of food-triggered AE*.	↑	

[1]1 Abstention

A therapeutic elimination diet is **recommended** after the individual diagnosis of food allergy or food–induced eczema in AE.	↑↑	100%  (17/17) Expert Consensus

We **recommend** re-evaluation of a child's IgE mediated food allergy after one to two years after strict elimination diet.	↑↑	100%  (17/17) Expert Consensus

We **recommend against** general dietary interventions (e.g. other supplements, general avoidance of certain foods e.g. cow´s milk, gluten) for the management of AE.	↓↓	100%  (19/19) Expert Consensus

We **cannot make a recommendation** on probiotics for the management of AE.	0	100%  (19/19) Expert Consensus

We **recommend against** vitamins as a treatment for AE.	↓↓	100%  (17/17) Expert Consensus

Food allergens, pre- and probiotics

Food allergy has been documented in approximately one-third of children with moderate-to-severe AE.[364, 365] 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.[366] In older children, adolescents and adults pollen-associated food allergy should also be taken into account.[367-369]

Response patterns to food allergens

Three different clinical reaction patterns in patients with AE have been described, depending on the type of symptoms and their time of onset.[366, 370]

Immediate-type, non-eczematous reactions are usually IgE-mediated, occur within a maximum of 2 hours after the administration of the allergen, with skin manifestations such as urticaria, angioedema, flushing and pruritus or other immediate-type reactions of the gastrointestinal tract, the respiratory tract or the cardiovascular system in the case of anaphylaxis. Cutaneous manifestations occur in 74% of patients. In addition, children might develop a transient morbilliform rash 6–10 h after the initial immediate reaction, disappearing within a few hours and considered as 'late-phase' IgE-mediated response.[370, 371]

Isolated eczematous delayed-type reactions typically occur 6–48 h after the ingestion of the allergen, including flares of eczema in predilection sites of AE. However, such isolated eczematous reactions are rare.[367]

A combination of the two above-mentioned patterns with an immediate-type reaction followed by an eczematous delayed-type reaction has been described in approximately 40% of children with food and adolescents /adults with birch pollen associated reactions.[369, 372]

Sensitization to food should be identified by means of a detailed clinical history in combination with *in vivo* tests (skin prick tests - SPT) and *in vitro* tests (serum-specific IgE), as described in detail in food allergy guidelines.[373] *In vitro* tests are particularly valuable when SPT material for certain food is not available for routine diagnostics or when SPT cannot be applied (e.g. dermographism or UV- and drug-induced skin hyporeactivity, widespread eczema, or the inability to stop antihistamines). Moreover, *in vitro* specific IgE to food allergens may give better quantitative data for the grade of sensitization, which helps to estimate the probability of the risk of a clinical reaction. However, precise decision points are not available, but it offers the opportunity to test single recombinant allergens, which may have a better diagnostic specificity than testing with food extracts for some foods (e.g., Gly m 4 in pollen-related soya allergy, Ara h2 in peanut allergy).

Atopy patch tests (APT) are not considered a routine instrument since standardised test materials are still not available. APT are performed with self-made food material using a 1/10 dilution in saline of the fresh food applied for 24–48 h on non-lesional skin.[374] So far, APTs have demonstrated to improve the accuracy of skin testing in the diagnosis of allergy to cow's milk, hen's eggs, cereals and peanuts in patients with AE.[375-378] Whereas immediate-type reactions are associated with SPT positivity, delayed reactions are related to positive responses to APTs. However, double-blind placebo-controlled food challenge (DBPCFC) remains the 'gold standard' for the diagnosis of food allergy.[373]

Oral food challenge should be performed under medical supervision with emergency equipment available, particularly after long-term removal of the culprit food from the diet. Home introduction for

cow's milk may be considered in the absence of evidence of sensitisation and without active eczema. In practice, oral food challenge should be performed according to standardized protocols.[379] In AE, the major flaw is that it might not offer the opportunity to exclude placebo reactions or coincidental influences of other trigger factors of AE during the challenge period. Therefore, the evaluation of delayed reactions after 24 h or 48 h by trained personell is mandatory.[372, 373] Challenge tests based on repeated exposure to food enable the assessment of delayed adverse responses.[372]

All foods that are associated with immediate reactions should be avoided. It is suggested, however, to re-evaluate cow's milk and hen's egg allergy in infants and young children with AE after one to two years, as these might have been outgrown. According to the the Milk Allergy in Primary (iMAP) Care guideline reintroduction of cow's milk should be between 9-12 months of age or at least 6 months after diagnosis is made: https://gpifn.files.wordpress.com/2019/10/imap-treatment-algorithm.pdf.

In a systematic review[380], eight randomized controlled studies examined the effect of an elimination diet on existing AE. Based on this, there is no convincing evidence that a cow's milk- or hen's egg-free diet is beneficial in general, when unselected groups of patients with AE were studied. There is also no evidence for a benefit in the use of elementary or few food-restricted diets in unselected patients with AE. This comes with the caveat that elimination diets are difficult to carry out even in a motivating atmosphere during a clinical study and the dropout rate in AE studies is particularly high in studies on diets.

A Cochrane systematic review based on nine randomized controlled trials concluded that eliminating hen's egg from the diet in those who had evidence of significant sensitisation to hen's egg proved beneficial to AE control.[381] Accordingly, the American Academy of Dermatology recommends hen's egg restriction in the subset of patients with AE, who were found to be clinically allergic to hen's egg.[382] This approach should also be followed for other food allergens proven relevant in individual patients.

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.[383] Other studies failed to show significant effects.[384, 385] 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.[386] A recent Cochrane review identified 39 randomised controlled trials involving 2599 randomised participants.[387] 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.[388]

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.[389]

Vitamins

A double blind, randomized clinical trial evaluated the effects of multistrain synbiotic (prebiotic+probiotic) versus vitamin D3 supplements or conventional therapy (topical steroid, emollients, antihistamine) on the severity of atopic eczema among 81 infants under 1 year of age for a period of two months; results showed a significant difference in SCORAD reduction between synbiotic

(p<0.001) and vit D3 (p=0.001) groups compared to control group and no significant difference between vit D3 and synbiotic groups (p=0.661).[390]

In another randomized, controlled, investigator -blinded study on 26 young patients a product containing Licochalcone A lotion (LA+omega6+ceramide3+glycerin) was compared with an hydrocortisone lotion twice daily for 4 weeks in an intrapatient comparison. A significant reduction of SCORAD was observed in the LA side (p<0.001), but no statistical significant difference between the two sides (p=0.199) were found. Relapses were lower in the LA side; patients satisfaction was high with both therapies but HC lotion induced a faster resolution of oedema, erythema, excoriation and pruritus (no statistical difference between two sides).[391]

The effects of pre-natal folic acid and iron supplementation was studied by administering standardized questionnaire to 344 women who delivered babies in an Italian hospital. Women were supplemented before childbirth with iron only, folic acid only, iron+folic acid or no supplements. Results of this study showed that iron+folic acid supplementation during pregnancy had protective effect for AE in the offspring while smoking during pregnancy and family history of AE increased risk of AE in the offspring. No association between AE and body mass index, psychological distress condition, maternal food antigen avoidance during pregnancy, vegetables and fruit as antioxidants intake was found.[392]

14. Allergen-specific immunotherapy

We **recommend against** allergen-specific immunotherapy as a routine treatment option for AE.	↓↓	>50%  (8/13) Expert Consensus
We **suggest** that AIT is considered for selected patients with aeroallergen sensitization and a history of clinical exacerbation after exposure to the causative allergen	↑	100%  (11/11) Expert Consensus

Introduction

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 idea behind it is that an immune tolerance is achieved in the sensitized patient by modifying the immune response and re-gaining regulatory capacities of humoral and cellular immune components.[393] Such changes may lead to the clinical improvement of allergic symptoms, reduced use of symptomatic rescue medications and improve QoL. The first promising and successful results were established and published in 1911.[394]

According to recent recommendations, ASIT is advised for a minimum period of 3 years, however according to long-term efficacy data, the longer the treatment the better. For AIT purified, non-allergenic, highly-immunogenic modified allergen extracts have been recommended. The routes of AIT may be of sublingual, oral, subcutaneous, or even transdermal and intralymphatic forms have recently been introduced.[393] Among these the sublingual (SLIT) and subcutaneous (SCIT) ways of application are the most commonly used forms, both being equally efficacious and safe, however SLIT formulation ensures greater liberty for the patient, while the SCIT secures better compliance and treatment adherence. Both SCIT and SLIT have seen low overall therapy compliance as well as varying levels of treatment literacy. In one meta-analysis, SCIT discontinuation ranged from 6 to 84% whereas SLIT discontinuation ranged from 21 to 93%.[395]

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.[5]

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

AIT consists of administering increasing doses of allergen in order 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 .

Favourable effects of AIT on disease symptoms of AE appear to be higher if accompanying relevant type I sensitizations are present, but only house dust mite-sensitized patients have been studied in larger studies in AE patients.

Here, the data for subcutaneous immunotherapy are stronger when compared to sublingual therapy and patients with severe AE (SCORAD > 50) showed better results.[396]

Systematic Reviews

In recent years, different attempts to perform systematic review and meta-analysis on ASIT in AE were made. The first systematic review of the literature analyzed 10 studies in 2007 [distinguishing among placebo-controlled and observational studies].[397] The authors concluded that the overall effect was in favor of AIT, but no conclusion and recommendation could be formulated at that moment. In 2013 Bae et al.[398] performed a meta-analysis including 8 studies. The authors concluded that their meta-analysis provided moderate-level evidence for the efficacy of SIT against atopic dermatitis. They stated however that there is only a moderate quality of the evidence supporting the use of AIT.

Gendelman and Lang[399] analysed the double-blinded controlled trials published about SCIT and SLIT until 2013, including 8 studies, using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. Based on finding serious methodological problems, the authors concluded that only a weak recommendation could be given for use of AIT in patients with AE.

There has been recent data published on the efficacy of adjuvant SLIT treatment in AE patients in a small pilot study. The results indicated good efficacy and clinical response in mild-to-moderate AE. Furthermore AIT improved skin permeability barrier functions as well.[400]

Finally, a Cochrane systematic review was published in 2016.[401] The authors included 12 studies and stated that this small number of studies was insufficient to give conclusive results .

The most recent guidelines of dermatological societies suggest to evaluate AIT in patients with AE and sensitization to aeroallergens, and not fully responding to symptomatic treatment, leaving the final decision to the clinician

AIT prescription should be considered individually for each patient, evaluating the risk/benefit ratio, and discussed with the patient.[402]

Based on this evidence, we **suggest** that AIT may be considered for selected patients with house dust mite, birch or grass pollen sensitization, and a history of clinical exacerbation after exposure to the causative allergen or a positive corresponding atopy patch test. Moreover, AIT shall be applied in patients with respiratory atopic diseases and an approved indication of that therapeutical procedure with AE as a comorbitidy.

15. Complementary medicine

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

Introduction

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 and others.

Acupuncture

Acupuncture has been widely applied for the treatment of many chronic diseases, especially dermatological conditions.[403, 404] Some clinical trials have demonstrated that acupuncture can significantly reduce itch intensity and allergen-induced basophil activation in patients with AE.[405, 406]

A recent systematic review by Jiao et al[407] included eight RCTs (with 434 participants) compared the efficacy of acupuncture versus no treatment/placebo/conventional medicine in patients with chronic eczema. One included RCT showed that acupuncture was better than no treatment at reducing itch intensity but the results were not considered as reliable because of the low number of patients included (10 patients). The combined results of six RCTs showed that acupuncture was better than conventional medicine at reducing the eczema area and severity index (EASI) and the combined results of seven RCTs showed that acupuncture was better than conventional medicine in terms of global symptom improvement in AE. A meta-analysis of six and seven RCTs found a reduction in EASI (MD: −1.89, 95% CI: −3.04 to −0.75, I^2: 78%) when acupuncture e was compared to conventional medicine, and in global symptom improvement (RR: 1.59, 95% CI: 1.20 to 2.11, I^2: 55%), respectively. No data on QoL and AE recurrence rate were available. No severe adverse events were found related to acupuncture.

The certainty of evidence of all outcomes was graded as low, because of high risk of bias, too small sample sizes and indirectness (due to studies having included patients with chronic, not explicitly atopic, eczema). The effects of acupuncture may have been exaggerated in these trials.

Phytotherapy

We searched for studies examining the efficacy of phytotherapy in atopic eczema and we found only four studies including a small number of patients.

Fermented rice flour containing Lactobacillus paracasei CBA L74 (heat-killed probiotic lactobacilli) 7g/day diluited in a liquid in 10 young patients (6 months-6 years old) for 12 weeks in combination with topical corticosteroids and emollients was able to reduce the need of steroid application in half of the patients and the stop of steroid application in the other half.[408]

A single-center, open-label, pilot study on 20 adult patients with moderate-severe AE found that the application of a cream containing SOD 100000IU+combination of plant extracts twice daily in monotherapy for 30 days decreased the overall SCORAD of 67% from baseline.[409]

A double-blinded, randomized, placebo-controlled trial on 45 pediatric patients compared the efficacy of a cream containing an extract of Ficus carica L. (Melfi cream) versus hydrocortisone or placebo: both Melfi cream and hydrocortisone cream after 14 days of application determined a significant reduction of SCORAD compared to placebo.[410]

In another controlled study the efficacy and skin biophysiology of a cream and cleanser containing lipid complex with shea butter extract was compared with a ceramide product on a total of 58 AE patients,

for 4 weeks of therapy. The treatment was well accepted, with improvement of SCORAD values and DLQI but no significant differences between the two products were found.[411]

There is lack of well defined RCT and it should be noted that plant extracts may cause contact sensitization.[412]

Autologous Blood Therapy

A randomized double-blind placebo-controlled trial on 22 patients evaluated the clinical efficacy of intramuscular autologous plasma therapy and autologous high-molecular-weight plasma protein fraction therapy (AHPT) for 8 weeks in adult patients with recalcitrant atopic eczema. At the end of treatment patients in the AHPT group had a significant reduction in SCORAD and DLQI; no significant changes in the autologous plasma therapy group. Long term results were not maintained in either AHPT or autologous plasma therapy group.[413]

In another trial including 16 AE patients sensitized to HDM (Dermatophagoides farinae) the effects of intramuscular administration of autologous total immunoglobulin G twice weekly for 4 weeks were evaluated. Results showed a significant reduction of specific IgE and increase in specific IgG, showing a potential anti-allergic immunomodulatory effects in AE patients of autologous total IgG injections. No adverse events were declared.[414]

Long-term changes of clinical severity and laboratory parameters after intramuscular autologous IgG (Autologous ImmunoGlobulin Therapy: AIGT) for 4 weeks were studied in 3 AE adult patients and followed up for 2 years. In all cases a clinical improvement and a decrease in IgE levels were seen, with one patient who experienced a clinical improvement at week 40 until the end of follow up and the other two patients who had faster clinical improvement but a shorter duration of the response.

Authors concluded that AIGT had long-term favorable effects on both clinical severity and laboratory parameters in selected patients with severe recalcitrant AE.
No adverse events emerged during the observation period.[415]

There is only very limited evidence supporting autologous blood therapy in the treatment of AE.

Chinese herbal medicine

Chinese herbs have traditional been used in Chinese medicine for many years.

Recent systematic reviews could not find conclusive evidence to demonstrate that topical application of CHM for AE was superior to other control interventions due to methodological weaknesses of the included randomised controlled trial[416] and could not find conclusive evidence that CHM taken by mouth or applied topically to the skin could reduce the severity of eczema in children or adults.[417]

Well-designed, adequately powered RCTs are needed to evaluate the efficacy and safety of CHM for managing eczema.

High altitude alpine climate

Fifteen observational studies were included in a recent review concerning 40.148 patients. Four studies concerning 2.670 patients presented follow-up data over a period of 1 year.[345] Quality assessment showed serious study limitations, therefore resulting in a very low level of evidence for the described outcomes.

Patient characteristics were not well described, and data on other pharmacological therapy were not provided. In most studies, style of reporting was very global and details were often lacking, making it difficult to interpret the data. Because no trials have been conducted and no control groups were included in the observational studies, there is no reliable data on which elements of alpine climate treatment are responsible for the observed effect.

The results of this systematic review provide very low quality evidence that alpine climate therapy results in decreased disease activity and reduced corticosteroid requirement.

A small study including 7 patients with atopic eczema, who spent 5 days in a moderate altitude mountain region, reported no changes in SCORAD.[418]

16. Psychological and educational interventions

We **suggest** that therapeutic patient education programmes with proven efficacy in children and adults with AE are widely implemented.	↑	100%  (14/14) Expert Consensus

Introduction to therapeutic patient education (TPE)/ complex 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.[419] Stress can elicit severe exacerbations of the disease and perpetuate the itch-scratch cycle. Anxiety or depression are acknowledged comorbidities in AE patients.[420] Furthermore, poor QoL and adherence to treatment are key issues in these patients.[421] As a multidimensional phenomenon, low treatment adherence is influenced among others by 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.[421] 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 behavioral therapy techniques) from a trained healthcare professional to the patient or their parents.[422] Additionally, as TPE is a patient-centered 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.[423]

High-quality TPE programmes should ideally be evidence-based, tailored to patient's needs, taking into account the individual educational and cultural background (rather than being standardized in form and content). It should also have a well-defined content and activities that are provided by an interdisciplinary health care team.[424]

In terms on efficacy on disease severity outcomes, a recent meta-analysis including 7 RCTs that evaluated the effect of parental education with a total of 1853 children showed a significant difference in the SCORAD scores between the TPE and non-TPE groups (standardized mean difference = - 8.22, 95% CI = - 11.29, - 5.15; $p < 0.01$).[425] The quality of evidence was assessed by Grading of Recommendations Assessment, Development and Evaluation (GRADE). However no significant differences in terms of QoL between groups were identified. A wide variety of interventions programmes are used depending of cultural backgrounds and health care systems (individual psychosomatic counseling, individual nurse or psychologist-led sessions, single or multiple interdisciplinary group sessions, written action plans, lectures, online videos etc.) and optimal delivery mode needs to be determined.[426] Although evidence remains limited regarding the efficacy of each of these interventions in the management of AE, the best

efficacy results and level of evidence are provided by interdisciplinary well structured age related group programmes in adults and children.[424, 427]

Nurse or psychologist-led programmes

There is some evidence that eczema workshops lead to an improvement in severity scores with greater adherence in AE management, itch-scratching cognition, and additional psychological benefit.[424] Nurse led programmes result in more effective use of topical therapies, improvement of severity scores and may be sparing doctor's time compared to standard care.[428] The relative effectiveness of nurse led programs compared to multidisciplinary age related, structured programmes is unclear.

E-health

There is some evidence that a direct-access, online model for follow-up dermatologic care is equivalent to classical in-person care in terms of efficacy but less costly.[426]

Other approaches

As adjunctive therapies and in order to cope with AE, different psychological interventions can be useful. They can have a positive effect on the severity of the disease and on itching and scratching behaviors. A systematic review including 8 RCT, revealed that 5 showed a significant reduction in eczema severity.[429] Autogenic training (a systematic form of relaxation involving increasing awareness of the body), cognitive-behavioral therapy, habit reversal and behavioral therapies seems to be more effective rather than aromatherapy, brief dynamic psychotherapy and stress management programme. An effect on itching intensity has been found in all different kind of interventions evaluated except for habit reversal behavioral therapy.

Conclusion

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-behavioral therapy, habit reversal and behavioral therapies have a positive effect on different aspects of AE.

17. 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 data on the efficacy and safety in this patient population. On the other hand, 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.[132] There are no major clinical differences between classical AE worsening and AEP. Physiological skewness of the immune system towards a Th2-dominated 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 during pregnancy to avoid presumed harm to the fetus.[430] 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.

17.1. Pregnant women

In pregnant women with AE, we **recommend** TCS class II or III.	↑↑	100%  (19/19) Expert Consensus
In pregnant women with AE, we **suggest** that TCI may preferably be used 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.	↑	100%  (19/19) Expert Consensus
In pregnant women with AE, when topical treatments are insufficient, we **recommend** narrow-band UVB (311 nm) or broad spectrum UVB therapy if NB-UVB is unavailable.	↑↑	100% 

		(19/19) Expert Consensus
In pregnant women with AE, who are candidates for systemic treatment, we **suggest** ciclosporin.	↑	100%  (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.	↑	100%  (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.	↓↓	100% 
In pregnant women with AE, we **suggest** prednisolone only as short term rescue therapy for acute flares.	↑	(16/16) Expert Consensus
In pregnant women with AE, we **recommend against** the use of abrocitinib, baricitinib, upadacitinib, methotrexate and mycophenolate.	↓↓	100%  (15/15) Expert Consensus

In pregnant women with AE, we **cannot make a recommendation** regarding the use of dupilumab and tralokinumab during pregnancy due to the current lack of clinical data.	**0**	100%  (15/15) 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.[36]

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, foetal death, and low Apgar score, although the use of very potent topical corticosteroids may be associated with low birthweight.[431] 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 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.[132]

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 narrow-band 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.[431] Only short courses of prednisolone (maximum 0.5mg/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 fails, 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 placenta[432] and should not be used during pregnancy, unless the potential benefit to the mother justifies the potential risk to the foetus.

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.[132]

MTX and mycophenolate mofetil are teratogenic and therefore strictly contra-indicated during pregnancy.

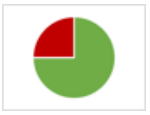
We cannot recommend any of the novel systemic medications, as there is currently no clinical data available to inform about any potential drug-associated risks. On the other hand, pre-clinical data does not indicate that there would be a teratogenic potential of dupilumab or tralokinumab if given during pregnancy.

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

17.2. Specific consideration for breastfeeding women

In breastfeeding women with AE, we **recommend** TCS II or III.	↑↑	>75%  (14/15) Expert Consensus
In breastfeeding women with AE, we **suggest** prednisolone only as short-term rescue therapy for acute flares.	↑	
In breastfeeding women with AE, we **suggest against** abrocitinib, baricitinib, upadacitinib, azathioprine, ciclosporin and methotrexate.	↓	
In breastfeeding women with AE, we **cannot make a recommendation** regarding the use of dupilumab and tralokinumab due to the current lack of clinical data.	0	

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.[132]

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.[132]

17.3. Family planning

In parents with AE planning to have a child, we **recommend** TCS II or III or TCI.	↑↑	100%  (22/22) Expert Consensus

In women with AE planning to have a child, we **recommend** stopping methotrexate at least 3 months before conception.*	↑↑	>75%  (13/14) Expert Consensus
In men with AE planning to have a child, we **recommend** stopping methotrexate 3 months before conception.*	↑↑	

*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. 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.[132]

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

18. Considerations for paediatric and adolescent patients

Important phenotypic and diagnostic differences

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 either represent with AE or hand eczema as adults.[433]

Severe early disease and a family history of AE may predict a more persistent course of the disease.[37]

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.[434]

Prematurity causes barrier dysfunction with higher transepidermal water loss (TEWL) and increased percutaneous absorption of chemicals. This is an important factor at 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 also 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 is changing with age, avoiding harsh soaps and detergents and using bath emollients to aid skin hydration and emollients as soap substitutes to aid barrier function.[435]

Wet wraps can be a useful treatment approach where additional hydration of the skin is needed, in particular in young children. [72]

Prevention

In children with AE we suggest to pay particular attention to emerging concomitant allergic diseases. About half of patients with moderate-to-severe AE develop food allergies (FA), asthma, and allergic rhinitis.

Skin care interventions, such as the regular use of emollients during the first year of life, have not shown convincing evidence of a reduction in AE development up to 2 years of age (see also emollient section).

Topical anti-inflammatory treatment

As for adults, a stepped approach of TCS potency is recommended. Mild potency TCS is typically sufficient for mild atopic eczema in the face and neck (for 5-7 days). Moderate potency TCS are used for moderate atopic eczema, and potent for severe atopic eczema. Moderate or potent preparations are used for short periods (7 to 14 days) for flares. In vulnerable sites such as axillae and groin, less potent topical corticosteroids or TCI are desirable. Topical corticosteroids are recommended to apply once or twice daily for children under 12 years. Adolescents and adults will generally be instructed to apply a topical steroid 1-2 times a day for short bursts of treatment, and then stop or step down use when the

AE flare-up settles. Potent or very potent topical corticosteroids in children aged under 12 months should only be applied under specialist dermatological supervision.[38]

TCS are applied once or twice daily to all the affected areas, one of the times ideally shortly after a bath. The most common way to measure the amount of medication needed is by fingertip unit (FTU). This means the amount of medication that covers the finger from its tip to the first joint.

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.

With mild disease activity, maintenance use of topical corticosteroid twice to thrice weekly (monthly amounts in the mean range of 15 g in infants, 30 g in children and up to 60–90 g in adolescents and adults, adapted to affected body surface area) with a liberal use of emollients do not result in adverse systemic or local effects.[37]

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 (Ref. 349). Daily application (BID) recommended during relapses on the affected area, following the FTU rules, while according to the pro-active regimen they may also be applied twice a week on the symptom-free areas.[37] TCI are also used off label under 2 years of age in many centres.

19. Occupational aspects

AE can have a negative impact on work life and is associated with a higher risk of hand eczema.	**State-ment**	100%  (15/15) Expert Consensus

We **suggest** individual pre-employment counselling regarding choice of profession, including risk assessment, avoidance strategies and protective measures.	↑	100%  (23/23) Expert Consensus

A number of occupational aspects are relevant to AE patients, as they are running a significant risk of developing occupational contact dermatitis. Atopy amplifies the effects of irritant and allergen exposure in several professions such er hairdressers, nurses, metalworkers, mechanics and cleaners, where hand eczema is a very common disease.[5] The risk for hand eczema in AE patients is increased about 4-fold.[436] 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.[5]

Impact of atopic eczema on work life

AE has an adverse impact on QoL of patients and families, but may also impact work life and career choice. Knowledge is scarce though the socio-economic and individual costs due to loss of work activity is likely to be considerable.

The systematic review of Nørreslet et al. examined the literature up to February 2017 regarding impact on work life for AE patients, with a specific focus on choice of education and occupation, sick leave, change of job and disability pensions due to AE.[437] No meta-analysis could be performed due to wide methodological heterogeneity of included publications. Quality assessment was performed by the authors based on a validated list of criteria.[437] 23 papers were found eligible, including 26 studies with 103,343 participants from 12 different countries comprising 7.789 AE patients. Supplementary Table 4 provides an overview of these 26 studies.

Influence on job choice

Out of five studies on the influence of AE on job choice, only one study in three of moderate/high quality showed significant influence on job choice.[438-440] Two studies of low quality demonstrated influence on job.[441, 442] Thus, no consistent conclusion can be drawn.

Influence on sick leave

For the nine studies on sick leave, only one was of moderate/high quality,[443] the rest of low/moderate quality.[440, 441, 444-449] Sick leave was assessed indirectly as work-loss costs, lost work productivity or days away from work. In all studies sick leave was self-reported, proposing a risk of recall bias. Eight out of nine studies found increased sick leave due to AE.[440, 441, 444-449]

Social compensations due to AE

The two low quality studies on social compensations showed a negative impact.[441, 450]

Influence on work life

For the twelve studies assessing influence on work life due to AE, nine were of moderate or moderate/high quality[440, 443, 451-457] and three of low/moderate or low quality.[458-460] Objectives, outcomes and study designs were very heterogeneous. Overall, three studies reported significant influence of AE on change or loss of job,[440, 451, 459] while five reported no marked association.[443, 452, 455, 456, 460] The remaining studies did not assess this outcome.

This systematic review strongly suggests that AE negatively affects sick leave and possibly also job choice, change or loss of job and disability pensions.

After publication of the systematic review by Nørreslet et al.,[437] several studies have been undertaken regarding the economic burden of AE. All studies report similar results with reduced work productivity and activity in AE patients.[7, 461-466] One study estimated annual costs of productivity loss at $2400 higher for employed US adult AE patients vs. employed non-AE controls.[461] A Dutch study estimated costs of productivity loss at €6886 per patient per year (PPY) for controlled AE patients and €13.702 PPY for uncontrolled AE patients.[463]

Risks in atopic eczema patients when starting / during work life

Apart from the risks mentioned above, another risk when starting or during work life may be the onset of hand eczema (HE). Ruff et al. conducted a systematic review and meta-analyses to establish the association estimate between AE and the point, 1-year and lifetime prevalence of HE compared to controls.[436] Thirty-five studies were included with 168.311 participants, of which twenty-six in the meta-analyses with 90.336 participants. Of these 26, 10 were considered of high quality, 15 of moderate quality and one of low quality.

Prevalence of HE was significantly increased and associated with AE (point prevalence OR 2.35 (95% CI 1.47-3.76), 1-year prevalence OR 4.29 (95% CI 3.13-5.88), lifetime prevalence OR 4.06 (95% CI 2.72-6.06)). Positive significant associations between AE and occupational HE were found (1-year OR 4.31 (95% CI 2.08-8.91), lifetime prevalence OR 2.81 (95% CI 2.08-3.79)). In general population studies these results were confirmed (1-year prevalence of HE in individuals with and without AE - OR 4.19 (95% CI 3.46-5.08), lifetime prevalence OR 5.69 (95% CI 4.41-7.36)).

The systematic review was limited by different methods to diagnose both AE and HE (questionnaires versus clinical observation; only 5 of 26 studies used the validated U.K. working party's diagnostic criteria; risk of misclassification), lack of prospective studies for 1-year and lifetime prevalence of HE (only through questionnaires; risk of misclassification, reporting bias) and poor clinical phenotype descriptions.

Based on this systematic review AE patients have a three- to four-fold increase in prevalence of HE compared to controls. Therefore, special attention and individual guidance should be given to AE patients, both prior to and during active work life and when affected by occupational HE.

Atopic eczema and counselling regarding work life

Several studies provide recommendations regarding counselling and follow-up of workers with AE,[437, 464, 467] based on the findings that AE is associated with HE and with a negative impact on work life. Pre-employment counselling with special attention on risk communication, avoidance strategies (see chapter avoidance techniques in AE) and protective measures (including higher need of emollients, see chapter basic emollients and moisturizers) is advised. Above all, guidance is recommended to be given to AE patients to avoid professions with skin irritating tasks or with contact with sensitizing substances, especially in patients with a history of persistent or relapsing HE. This includes a range of professions with wet-work, frequent use of gloves and exposure to sensitizing compounds, a non-exhaustive list is presented in Table 4.[436-438, 451-453, 468, 469] Secondary prevention is important, including frequent medical follow-up of the course of symptoms over the first few years on the job.[469] In case of problems, referral to a health and safety officer can be helpful to relieve the disease burden. However, no specific studies in the AE population were found regarding the effectiveness of such primary and secondary prevention measures.

Table 4: Occupations with an elevated risk of hand eczema

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, fiberglass, 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, fiberglass, acids and alkalis, detergents
Mechanic and metal worker	cutting fluids, coolants, detergents, metals, petroleum products, preservatives

XI. 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, e 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 standardised 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 the systemic AE therapies.

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