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Thomas Werfel, Annice Heratizadeh, Werner Aberer, Matthias Augustin, Tilo Biedermann, Andrea Bauer, Regina Fölster Holst, Julia Kahle, Maria Kinberger, Katja Nemat, Irena Neustädter, Eva Peters, Ralph von Kiedrowski, Peter Schmid Grendelmeier, Jochen Schmitt, Thomas Schwennesen, Dagmar Simon, Thomas Spindler, Claudia Traidl-Hoffmann, Ricardo Niklas Werner, Andreas Wollenberg, Margitta Worm, Hagen Ott

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GUIDELINE

S3 Guideline Atopic dermatitis: Part 1 - General aspects, topical and non-drug therapies, special patient groups

Thomas Werfel[1] | **Annice Heratizadeh**[1] | **Werner Aberer**[2] | **Matthias Augustin**[3] | **Tilo Biedermann**[4] | **Andrea Bauer**[5] | **Regina Fölster-Holst**[6] | **Julia Kahle**[7] | **Maria Kinberger**[8] | **Katja Nemat**[9] | **Irena Neustädter**[10] | **Eva Peters**[11] | **Ralph von Kiedrowski**[12] | **Peter Schmid-Grendelmeier**[13] | **Jochen Schmitt**[14] | **Thomas Schwennesen**[15] | **Dagmar Simon**[16] | **Thomas Spindler**[17] | **Claudia Traidl-Hoffmann**[18] | **Ricardo Niklas Werner**[8] | **Andreas Wollenberg**[19,20] | **Margitta Worm**[21] | **Hagen Ott**[22]

Correspondence
Prof. Dr. med. Werfel Thomas, Department of Dermatology, Allergology and Venereology, Hannover Medical School, Carl-Neuberg-Straße 1, 30625 Hannover, Germany.
Email: werfel.thomas@mh-hannover.de

Summary
This S3 guideline was created based on the European S3 guideline, with special consideration of the medical conditions in the German-speaking region and incorporating additions from the previous German-language version. The interdisciplinary guideline commission consisted of representatives from the German Dermatological Society, the Professional Association of German Dermatologists, the

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Participating societies:

DDG – German Dermatological Society e.V.
BVDD – Professional Association of German Dermatologists e.V.
ÖGDV – Austrian Society of Dermatology and Venereology
SGDV – Swiss Society of Dermatology and Venereology
DGAKI – German Society for Allergology and Clinical Immunology e.V.
DGKJ – German Society for Pediatric and Adolescent Medicine e.V.
BVKJ – Professional Association of Pediatricians and Adolescent Medicine e.V.
GPA – Society for Pediatric Allergology and Environmental Medicine e.V.
DGPM – German Society for Psychosomatic Medicine and Medical Psychotherapy e.V.
German Network for Health Services Research e.V.
German Allergy and Asthma Association e.V.
DGpRP – German Society for Pediatric Rehabilitation and Prevention e.V.
AGNES – Working Group for Atopic Dermatitis Education e.V.
German Atopic Dermatitis Association e.V.
German Contact Allergy Group e.V.
Working Group Allergology of the German Dermatological Society
Working Group Health Economics and Evidence-Based Medicine of the German Dermatological Society
Working Group Occupational and Environmental Dermatology of the German Dermatological Society
Working Group Pediatric Dermatology of the German Dermatological Society
Working Group Allergology of the Swiss Society for Dermatology and Venereology

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Austrian Society of Dermatology and Venereology, the Swiss Society of Dermatology and Venereology, the German Society for Allergology and Clinical Immunology, the German Society for Pediatric and Adolescent Medicine, the Professional Association of Pediatricians and Adolescent Medicine, the Society for Pediatric Allergology and Environmental Medicine, the German Society for Pediatric Rehabilitation and Prevention, the German Society for Psychosomatic Medicine and Medical Psychotherapy, the German Network for Health Services Research, the German Eczema Association and the German Allergy and Asthma Association.
This first part of the guideline focuses on the definition and diagnostic aspects of atopic dermatitis (AD), addressing topical therapy as well as non-pharmacological treatment approaches such as UV therapy, psychoeducational therapy, dietary interventions for AD, allergen immunotherapy for AD, and complementary medicine. This part of the guideline also covers specific aspects of AD in children and adolescents, during pregnancy and lactation, and in the context of family planning. Additionally, it addresses occupational aspects of AD and highlights the perspective of the patients. The second part of the guideline, published separately, addresses the systemic therapy of AD.

KEYWORDS
atopic dermatitis, atopic eczema, eczema

INTRODUCTION

The present guideline is an update of the AWMF S2k guideline "Diagnosis and treatment of atopic dermatitis" published in 2015. The update was made by adaptation of the "EUROGUIDERM GUIDELINE ON ATOPIC ECZEMA" by Wollenberg A et al., published in its final form under https://doi.org/10.1111/jdv.18345 and https://doi.org/10.1111/jdv.18429, and also available on the website of the *European Dermatology Forum* (licensed under CC BY NC 4.0, https://creativecommons.org/licenses/by-nc/4.0/). Moreover, the adaptation basis of "*EuroGuiDerm guideline on atopic eczema*" was supplemented by updated and fundamental content and aspects of the previous German version of the S2k guideline "Diagnosis and treatment of atopic dermatitis" from 2015.[1] Several sections of the guideline have been adopted without changes from the previous versions.

The present guideline consists of two sections, published separately: Part 1 (this publication) addresses the general aspects of atopic dermatitis, local therapy, non-pharmacological therapeutic approaches, and special aspects in certain patient groups. Part 2 will focus on systemic therapies of atopic dermatitis. In both published sections, the recommendations are complete and unabridged while the content on medical background and available studies is presented in a shortened form. The unabridged long version of the guideline is available at the AWMF website (https://register.awmf.org/de/leitlinien/detail/013-027).

METHODS

Additional information is available in the guideline report or the long version of the guideline (www.awmf.org).

For the standardized presentation of the recommendations, the wording and symbols presented in Table 1 were used. For the national AWMF S3 guideline, all recommendations were again formulated and discussed, and a consensus was reached again.

Process of consensus formation

During digital consensus meetings on July 11, 2022, July 12, 2022, and August 31, 2022, a consensus concerning the proposals for recommendations was reached by means of a nominal group process. During voting on recommendations concerning systemic drugs, only experts without conflicts of interest (COI) voted.

External evaluation

An extensive external evaluation was performed during creation of the European guidelines. This included various national societies, representatives of pharmaceutical industry, and members of the *European Dermatology Forum*. The German version was approved after evaluation by the 2+2 committee of the German Dermatological Society and the

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TABLE 1 Strengths of recommendation – wording, symbolism and interpretation (modified in accordance to Kaminski-Hartenthaler et al., 2014[2]).

Recommendation strength	Wording	Symbol	Interpretation
Strong recommendation for a procedure	"… shall …"	↑↑	We believe that all or almost all informed people would make a decision in favor of this intervention.
Weak recommendation for a procedure	"… should …"	↑	We believe that most informed people would make a decision in favor of this intervention, but a substantial part would not.
Recommendation *open* / no recommendation	"… may be considered …"	0	Currently, no recommendation in favor or against this intervention can be made due to certain circumstances (unclear or balanced risk-benefit ratio, no evidence data available, etc.)
Weak recommendation *against* a procedure	„… should not …"	↓	We believe that most informed people would make a decision against this intervention, but a substantial part would not.
Strong recommendation *against* a procedure	„… shall not …"	↓↓	We believe that all or almost all informed people would make a decision against this intervention.

Professional Association of German Dermatologists, and the evaluation of all participating societies. Representatives of the pharmaceutical industry were not involved in the present German version.

Update/validity

It is the aim to create a *living guideline* by continuous updating in connection with the European guideline. Reference is made to potential updates that shall be published on the AWMF website.

GENERAL ASPECTS OF ATOPIC DERMATITIS

Definition and classification

In Germany, approximately 13% of all children and approximately 2% of all adults suffer at least temporarily from atopic dermatitis (AD).[3]

AD is a chronic or chronically relapsing, noncontagious skin disease usually associated with severe pruritus and with a classic morphology and location that differs in an age-dependent manner. The disease has different severities, with the majority of patients suffering from a milder form of AD. Depending on location and extent of AD (up to erythroderma), however, it may be a severe skin disease with significant and long-term impairment of quality of life. More common complications of AD include infections, such as disseminated impetiginization by *Staphylococcus aureus*, viral infections, or fungal infections.[4,5]

A significant proportion of the patients (50%–80%, depending on the study) exhibits IgE-mediated sensitizations against aeroallergens and/or food allergens that may be associated with allergic rhinoconjunctivitis, allergic asthma, or clinically relevant food allergy (extrinsic form of AD). This is differentiated from a form that may have an identical clinical picture, but shows no corresponding sensitization (non-allergic or intrinsic form).[6]

The treatment of AD and its complications requires qualified medical care. The skin disease itself and the factors associated with AD, especially the often almost unbearable pruritus, may result in impairment of quality of life, performance at school or work, as well as problems in the social environment and depression.

Epidemiology *(only background text without recommendations; see long version)*

Pathogenesis and genetics *(only background text without recommendations; see long version)*

Prevention (only background text without recommendations; see long version)

AD and vaccinations

Children, adolescents, and adults with AD *shall* be vaccinated regularly according to recommendations of the German Standing Committee on Vaccination (STIKO).	↑↑	100% consensus-based
In an acute exacerbation of AD, postponement of the vaccination until optimal stabilization of the skin condition *should* be considered.	↑	100% consensus-based

For background text, see long version.

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Manifestation

The different clinical manifestations of AD with their age-specific features and the most important differential diagnoses and comorbidities *shall* be familiar to the treating physicians.	↑↑	> 75% consensus-based

For background text, see long version.

Course

The patients *shall* be informed about the chronic and recurrent course typical of the age group, as well as realistic therapeutic goals.	↑↑	100% consensus-based

For background text, see long version.

Complications

Patients with AD and their relatives *shall* be informed (educated) about possible complications of AD.	↑↑	100% consensus-based

For background text, see long version.

Diagnostics

General aspects

As part of the general diagnosis, a comprehensive medical history (including personal, family, and occupational atopic history) *shall* be obtained.	↑↑	100% consensus-based
In patients with AD, the entire skin organ *shall* be examined.	↑↑	100% consensus-based
Depending on the severity, history, and course, possible psychosomatic, dietary, aeroallergenic, or environmental trigger factors *shall* be discovered in patients with AD.	↑↑	> 75% consensus-based
A biopsy for differential diagnosis of cutaneous lymphomas, in particular, *should* be considered especially in adult patients.	↑	100% consensus-based

General diagnosis requires a medical history (including personal and family atopic history) and the examination of the entire skin organ, including exact documentation. Moreover, it is necessary to identify potential psychosomatic, dietary, or other environmental trigger factors. A biopsy for differentiation of lymphomas and other differential diagnoses is only rarely required, and if so, usually only in adult patients. In children, this may be useful in individual cases with hypopigmented lesions. It must be stated, however, that AD cannot be distinguished with certainty from other eczema conditions by histopathology.

Well-defined diagnostic criteria for AD are important for scientific examinations, including controlled clinical studies. The diagnostic criteria published by Hanifin and Rajka (1980)[7] have become generally accepted in the international literature. They have, however, the disadvantage that the list of diagnostic criteria is very long, with 27 criteria in total. Given that their diagnostic specificity is only 78%, these criteria are not always sufficient to differentiate AD from another inflammatory dermatosis. An English working group developed its own diagnostic criteria (one major criterion and five secondary criteria) that have been validated for various patient collectives.[8] For questions concerning occupational dermatology, Diepgen et al.[9] have validated parameters for a so-called atopic dermal diathesis.

Comorbidity

Typical somatic (for example, food allergy, asthma, allergic rhinitis) and psychiatric (for example, depression, suicidal tendency) comorbidities of AD *shall* be considered during management of AD patients.	↑↑	> 75% consensus-based

For background text, see long version.

Differential diagnosis

In case of inconclusive AD based on history and clinical features or refractory disease course, both common and rare differential diagnoses *shall* be considered at any age.	↑↑	100% consensus-based
In case of eczemas involving hands and feet, atopic eczemas *shall* be distinguished from other eczema diseases (irritant toxic eczema, contact allergic eczema), palmoplantar psoriasis, tinea of the hands and feet, and palmoplantar keratodermas.	↑↑	100% consensus-based

For background text, see long version.

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Objective determination of severity

When using systemic therapies, objective disease severity and subjective disease symptoms, including quality of life, *shall* be documented initially and during therapy.	↑↑	100% consensus-based
Laboratory parameters (such as IgE, TARC, ECP) *should not* be measured in routine clinical practice to determine the severity of AD.	↓	100% consensus-based

For background text, see long version.

Diagnostic workup of allergies in AD: General approach

Individual allergy diagnosis *shall* be performed in patients with AD depending on findings and history.	↑↑	100% consensus-based
However, untargeted "allergy screening" in all patients with AD *shall not* be performed.	↓↓	
The clinical relevance of established sensitizations to food allergens for AD *shall* be determined individually by means of elimination and provocation tests.	↑↑	
Patch tests with protein allergens (known as atopy patch test) *shall not* be performed in routine diagnostics.	↓↓	
Patch tests with low molecular weight substances to reveal an additional contact allergy *shall* be performed in AD when suggested clinically or by the history.	↑↑	

Prick testing and/or measurement of specific immunoglobulin E (IgE) antibodies shall be considered in individual allergy diagnostics when suggested clinically or by the history. In infants with moderate to severe AD with a markedly increased risk of immediate-type food allergies compared to healthy peers, screening against basic food not yet consumed and tolerated without complications by the infant may be considered. The clinical relevance of sensitizations should be determined individually by means of elimination and/or oral provocation tests.

Patch tests with protein allergens (atopy patch test) shall not be performed in routine diagnostics.

The relevance of allergic reactions in AD must be verified individually. Often, sensitizations to numerous environmental allergens (for example, pollen, animal dander, dust mites, fungi, and food) are detected. For this purpose, prick tests and blood tests (detection of specific IgE antibodies) are available. The clinical relevance of sensitizations must be determined individually by means of elimination and/or provocation tests. Often, sensitization alone does not justify elimination or therapeutic measures.

Patch testing with low molecular weight contact allergens can reveal an additional allergic contact dermatitis in patients with refractory AD or a chronic disease course.

In patients with AD, the predisposition for increased skin irritation and the resulting increased rate of false-positive test reactions must be considered in patch testing. Depending on the chosen base for allergen preparation (for example, aqueous base) and concomitant exposure to additional, individually relevant aeroallergens, such as pollen, this may be of special relevance.[10–13]

Provocation factors of AD

Individual trigger factors of AD *shall* be identified in order to avoid or treat these factors with the aim of prolonged remission or clearance.	↑↑	100% consensus-based
In sensitized patients with AD, contact to aeroallergens *shall* be reduced as much as possible, if these have previously resulted in skin exacerbations.	↑↑	100% consensus-based
Physical activity *shall* not be restricted in patients with AD.	↑↑	100% consensus-based
Patients with AD *shall* avoid clothes irritating the skin (fabrics with rough, course fibers, such as wool).	↑↑	100% consensus-based
Patients with AD *should* learn strategies for stress management.	↑	100% consensus-based
If required, psychosocial consultation *shall* be provided, and psychotherapy *shall* be recommended, if indicated.	↑↑	
Tobacco smoke *shall* be avoided to prevent flare-ups of AD.	↑↑	100% consensus-based

For background text, see long version.

Disease costs

Treating physicians *shall* prescribe therapeutics without active ingredients with drug status (basic therapy) for children up to the age of 12 years (up to 18 years in those with developmental disorders) at the expense of the statutory health insurance.	↑↑	100% consensus-based

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Therapeutic management, general aspects

An individual treatment concept *shall* be developed depending on age, disease severity, psychosocial situation, provocation factors, and location of AD. For this purpose, a structured, understandable, written therapy plan is appropriate.	↑↑	100% consensus-based

The treatment of AD requires a variety of measures that should be adapted individually to each patient. This includes the reduction and avoidance of individual exacerbation factors, as well as individually adjusted, symptom-oriented basic therapy and topical and/or systemic, anti-inflammatory treatment. Therapy of the frequently agonizing pruritus presents a particular challenge.

Care structure: Interconnection of outpatient, inpatient, and rehabilitative care

In case of high severity, inpatient or partly inpatient treatment *shall* be considered.	↑↑	100% consensus-based
Depending of the treatment demand, outpatient or inpatient rehabilitation measures *shall* be offered to patients and their legal custodians.	↑↑	100% consensus-based
Participation in evidence-based, structured, interdisciplinary AD education, for example, according to the German AGNES curriculum (children and adolescents) or ARNE (adults), *shall* be recommended.	↑↑	100% consensus-based

For background text, see long version.

Multi-stage concept

The therapy of AD must be adapted to the different individual phases depending on severity and chronicity. Accordingly, the following step scheme (Figure 1) presents only a guide that shall be adjusted depending on age, disease course, location, and individual burden of suffering.

A step therapy adapted to the clinical manifestation *shall* be implemented in AD.	↑↑	100% consensus-based

TOPICAL THERAPY

Basic therapy with emollients and *moisturizers*

In patients with AD, gentle cleansing and bathing procedures *shall* be used, especially in acutely inflamed or superinfected skin.	↑↑	100% consensus-based
Showers and full baths in patients with AD *should* be performed as short as possible and with moderately warm water.	↑	100% consensus-based
Patients with AD *should not* use alkaline soaps. Patients with AD *should* regularly use care products without relevant irritants or contact allergens.	↓ ↑	100% consensus-based
Patients with AD *shall* use emollients as basic therapy of the disturbed skin barrier regularly and according to the needs.	↑↑	100% consensus-based
For basic therapy, patients with AD *should* use individually adapted topical agents, for example, more hydrophilic creams in summer and topicals with higher lipid content in winter.	↑	100% consensus-based
Patients with AD *shall* apply emollients immediately after a bath or shower and soft pad drying of the skin.	↑↑	100% consensus-based
In AD, emollients *shall* be used as basic therapy according to the needs even in remission-free intervals to avoid flare-ups and ameliorate symptoms.	↑↑	100% consensus-based

One of the characteristic features of AD is an impairment of the epidermal skin barrier function manifesting clinically as dry skin and promoting the penetration of allergens and other potentially harmful substances into the epidermis.[14]

One of the best-known anomalies is the mutation of filaggrin,[15] but other gene variants in the epidermal differentiation complex,[16,17] as well as changes in proteases and protease inhibitors and an altered composition of epidermal lipids (cholesterol, ceramides, free fatty acids) play also a role in the pathophysiology of the disease.[18–21] Moreover, several skin barrier molecules like filaggrin are downregulated in AD by cytokines of T helper 2 (Th2) cells causing regularly barrier defects in inflamed skin in AD.[22] The treatment measures to improve the impaired skin barrier function and maintain the normal function are often referred to as "skin care"; this includes measures to avoid irritant factors. It would be better to refer to "basic therapy of the impaired skin barrier function" instead of "skin care". The

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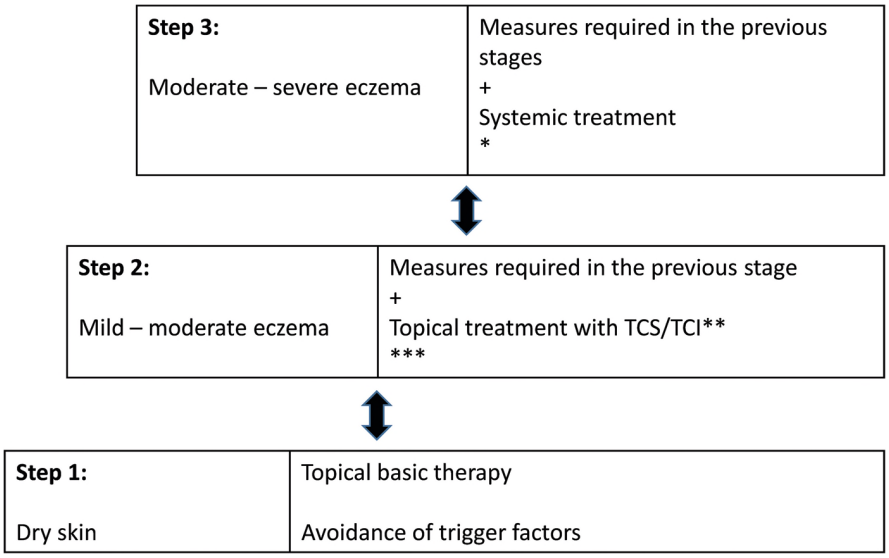

FIGURE 1 Stepped care plan for atopic eczema. For clarity, the figure does not include all the procedures discussed in this guideline. *UV therapy may be indicated from stage 3, particularly in adulthood. *Caution*: No combination of UV therapy with ciclosporin and topical calcineurin inhibitors. **First-line therapy: Usually topical glucocorticosteroids. In cases of intolerance or ineffectiveness and in specific locations (such as the face, intertriginous areas, anogenital region) use of topical calcineurin inhibitors. ***The additional use of antipruritic and antiseptic agents can be considered.

term "vehicle free of active substance" is often used for the treatment with emollients to distinguish it from pharmacotherapeutic procedures;[23–25] indeed, only few emollients are approved as drugs, but rather as cosmetic or medical products.[26–29]

The main principle of this basic therapy of the impaired skin barrier function is to supply the upper epidermis with lipids in order to restore the skin barrier.

Basic therapy with emollients

Basic therapy of the skin with emollients is central to each treatment of AD and should be maintained.[30,31] Emollients often contain *moisturizers* like urea or glycerol that promote the hydration of the stratum corneum and additional molecules that reduce the loss of water.

In this guideline, "emollients" are defined as "topical formulations with vehicle substances without active ingredients" while "emollients plus" signifies: "topical formulations with vehicle substances plus added active ingredients not classified as drugs".[32]

The application of emollients alone may be sufficient in individual cases with mild severity of skin inflammation. Acute flares shall generally be treated with anti-inflammatory substances, while at the same time (see also Chapter "Anti-inflammatory therapy") continuing the application of emollients as basic therapy. Usually, hydration of the skin is maintained by application of emollients with hydrophilic base at least twice a day.[25]

With respect to the galenic form of the formulation, seasonal differences should be considered apart from the preferences of patients and caregivers (higher hydrophilicity in summer, higher lipid content preferably in winter). The location of the affected body regions plays also a role (for example, paste for intertriginous areas, not too oily for the face).

For chronic lesions, lipophilic basic substances should be used to support the barrier.

The applied amount of the topical agent plays a crucial role in basic therapy. It can be based on the *fingertip unit* rule: a *fingertip unit* (FTU) is the amount of ointment expressed from a tube with a 5-mm-diameter nozzle measured from the distal skin crease to the tip of the index finger (approximately 0.5 g); this is an adequate amount for two adult palm areas corresponding to approximately 2% of an adult body surface area.[24]

Due to the costs of a high-quality treatment with emollients low in contact allergens or potentially irritative substances, their use is often restricted: They are, in principle, non-prescription products and not refundable for adolescents aged 12 years and above. In addition, the quantities required are usually high (often, up to 250–500 g a week).[33] (See also disease costs.)

The use of pure oil products, such as coconut oil or olive oil instead of emulsions will dry out the skin and increase the transepidermal water loss.[34]

Safety

The use of emollients alone in patients with indication for topical anti-inflammatory treatment poses a considerable risk for dissemination of bacterial or viral infections typical for AD.[35]

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Emollients may be associated with irritant and allergic side effects. Emollients may contain ingredients that can cause contact sensitization, such as emulsifiers, preservatives, and fragrances.[12,36–38] Depending on the affected body region, patients with "sensitive skin" may experience local irritations like stinging or burning sensation.[39] Given that the skin compatibility of topical formulations varies significantly between individuals, this aspect needs to be considered when treating patients with AD.

Urea may cause skin irritation in infants and should, therefore, be avoided in this age group. Toddlers should be treated with lower concentrations of urea than adults. Glycerol seems to be better tolerated than urea and sodium chloride.[30]

Propylene glycol may cause skin irritation in children younger than 2 years.

Bath oils shall not contain any allergenic proteins. Peanut and coconut formulations may increase the risk of sensitization. Allergenic proteins are usually no longer included in care products with refined oils.[40]

For additional aspects of this chapter, see long version.

Anti-inflammatory therapy

Topical glucocorticosteroids (TCS) *shall* be used as anti-inflammatory agents for the treatment of AD.	↑↑	100% consensus-based
Topical calcineurin inhibitors (TCI) *shall* be used as anti-inflammatory agents for the treatment of AD.	↑↑	
The "*fingertip unit* rule" *should* be used for the application of topical anti-inflammatory agents and be explained to the patients.	↑	100% consensus-based
TCS inhibitors *shall* be used for the treatment of acute flares in AD.	↑↑	100% consensus-based
Concerns or fears of patients or their legal custodians about glucocorticosteroids *shall* be adequately addressed.	↑↑	100% consensus-based
Given the profile of adverse drug effects of TCS, TCI *shall* be used in problem areas (face, intertriginous areas, anogenital region) as preferred long-term therapy.	↑↑	100% consensus-based
TCI *shall* be used in case of non-response or contraindication to TCS.	↑↑	100% consensus-based
A proactive therapy (usually twice weekly) with a suitable TCS or a suitable TCI (see background text) *shall* be performed according to the needs to reduce the risk of recurrence.	↑↑	100% consensus-based

An effective topical therapy is dependent on three fundamental principles: sufficient potency of the active ingredients, sufficient dosage, and correct application.[41] In Europe, glucocorticosteroids (TCS) and calcineurin inhibitors (TCI) are currently approved as topical anti-inflammatory therapies.

In topical anti-inflammatory therapy, a distinction is made between reactive and proactive management. In reactive treatment, the anti-inflammatory compound is applied to the visible skin lesions and discontinued after resolution or almost complete resolution of the lesions. The proactive therapy represents a combination of a prespecified long-term therapy with an anti-inflammatory agent applied usually twice weekly to the previously inflamed skin areas and a generous daily application of emollients as basic therapy to the entire body.[42] The proactive treatment thus follows upon the reactive therapy of an acute flare after successful treatment of visible inflammatory lesions with a regular anti-inflammatory therapy. The duration of the proactive management is usually adapted to severity and persistence of the disease.[43]

Sometimes, patients with acute, erosive and oozing lesions will not tolerate topical application of creams or ointments and may be treated first with "wet wraps" until the oozing stops. If clinical signs of a superinfection are evident on the skin, an additional topical antiseptic therapy and in case of very pronounced symptoms also a systemic antibiotic therapy should be considered. Wet wraps with added active ingredients are highly effective in acute AD and improve tolerability. The treatment with wet-wrap dressings with diluted or low-potency glucocorticosteroids (group II, III, normal dilution: 1 : 3 – 1 : 10, application for several days is usually sufficient) is a safe crisis intervention for the treatment of severe and/or refractory flare-ups of AD, with temporary systemic bioactivity of the glucocorticosteroids as the only reported serious adverse effect.[44–47]

Topical glucocorticosteroids

Modes of action and efficacy

TCS are used as first-line therapy in a stage-adapted manner to treat acute and chronic inflammations of the skin in AD depending on the symptoms (especially pruritus and sleeplessness).[48,49] The lipophilic character and the low molecular weight of TCS enable good penetration into the skin and binding to a steroid receptor in the cytoplasm. The TCS-receptor complex acts as transcription factor with two-fold activity, that is, it reduces the synthesis of proinflammatory cytokines and increases the synthesis of anti-inflammatory mediators. TCS have an immunosuppressive effect, they downregulate numerous aspects of the immune response and inhibit, among others, T-lymphocyte functions.

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According to Niedner, the potency of TCS is divided into classes ranging from low potency (class I) to very high potency (class IV).[50] The classification according to Niedner is used in these guidelines. The US-American classification is different and distinguishes seven groups from VII (least potent) to I (most potent). Modern, di-esterified TCS (hydrocortisone buteprate, hydrocortisone aceponate, hydrocortisone butyrate, prednicarbate, methylprednisolone aceponate, mometasone furoate) have a pronounced anti-inflammatory effect, but no strong antiproliferative effect, and thus a low atrophogenic potential.[51,52]

Dosage: acute flare, short-term treatment, long-term treatment

When choosing a TCS, the galenic form of the formulation, the age of the patient, and the body area to which the compound will be applied should be considered in addition to the potency. Usually, TCS with low to moderate potency should be used in children. For an acute AD flare, adolescent and adult patients may also use potent TCS, and on palmar and plantar regions very potent TCS, for a short period under supervision of a medical specialist. Occasionally, potent and very potent TCS are also used in younger age groups under supervision of a medical specialist.

For the treatment of the face and especially of the periorbital region or other sensitive areas (wrinkles, neck), TCS should be used for as short a time as possible, and for only a few days, if at all, and only TCS with low to moderate potency (class I and II) should be employed.[53]

For mild disease activity, a low amount of TCS twice weekly (mean monthly amount in the range of 15 g for infants, 30 g for children, and up to 60–90 g for adolescents and adults, more or less adapted to the affected body surface area), in combination with a generous daily application of emollients, allows for an effective maintenance therapy.

Patients with moderate or severe AD may benefit from a long-term proactive treatment with a TCS of moderate to strong potency. It has been shown that the use of fluticasone propionate (TCS class III) or methylprednisolone aceponate 0.1% (TCS class II) twice weekly may result in a marked reduction of AD flares. Comparable experiences are also available for other class II and class III TCS outside of clinical studies.[48,49,54]

Safety

Systemic absorption of potent and very potent class III and class IV TCS is possible. They are more likely to result in suppression of adrenal function than compounds of the classes I and II. Given the positive benefit-risk relation, especially di-esterified class III TCS (mometasone furoate, fluticasone propionate) should be preferred.[52] Cases of significant adrenal suppression during long-term use of TCS are rare.[55] Ghajar et al. reviewed nine studies (n = 371) that measured the serum cortisol levels after two weeks of TCS application. For TCS with low to moderate potency, no risk of adrenal suppression was found after short-term use.[56] Fishbein et al. analyzed twelve studies with 2,224 children receiving TCS. In four of 157 recorded participants (3%), mild adrenal suppression was found.[57]

Local side effects of TCS include a variety of skin changes, usually in the form of skin atrophy, occurring more often with older glucocorticosteroids of the classes III and IV than with the newer di-esterified agents and with less potent class II TCS. Local skin changes manifest as visible thinning and wrinkle formation, development of telangiectasias (rubeosis steroidica), spontaneous scar formation (pseudo-cicatrices stellaires), ecchymoses, striae distensae (stretch marks), and hypertrichosis.[58] In rare cases, TCS may cause contact allergy that may be difficult to differentiate from AD.

A review of eleven studies found a prevalence rate of burning sensation, pruritus, irritation, or heat sensation after use of TCS in < 1% to 6% of the treated patients.[59]

In infants, incorrect use of highly potent TCS in the diaper area may result in granuloma gluteale infantum or even in iatrogenic Cushing syndrome.[60]

The risk of TCS-related eye complications seems to be low. The use of TCS on eyelids and in the periorbital area in adults with AD, even for longer periods, has not been associated with the development of glaucoma or cataract.[61] However, there are isolated case reports of an increase in intraocular pressure after topical application of TCS. Treating physicians should be aware of this potential risk.[62,63]

Incorrect long-term use of potent or very potent TCS (class III, IV) in the face may trigger rosacea-like dermatitis or perioral dermatitis, and the skin may become addicted to TCS (*red skin* syndrome or corticosteroid withdrawal syndrome). Characteristic features are persistent erythemas, as well as burning and stinging sensations, and have been observed primarily in the face and the genital area in women.[64]

For additional aspects of this chapter, see long version.

Topical calcineurin inhibitors

Modes of action and efficacy

Two topical calcineurin inhibitors (TCI) (tacrolimus ointment and pimecrolimus cream) are approved for the treatment of AD. In the European Union, pimecrolimus cream (1%) is approved from 3 months of age and above, tacrolimus ointment (0.03%) from 2 years, and 0.1% tacrolimus ointment from 16 years. TCI have an immunosuppressive effect, they reduce the activity of the phosphorylase enzyme calcineurin, thus inhibiting T-lymphocyte activation. The transepidermal penetration of TCI is lower compared to TCS.[65,66] TCI are a first-line

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therapy for sensitive skin areas, where application of TCS is likely to be associated with side effects, or in areas where side effects of TCS have already occurred. The efficacy of both active ingredients has been established in clinical studies for short-term use (3 weeks)[67,68] and long-term use of up to one year compared to vehicle.[69,70]

In adults, proactive long-term treatment for a period of 12 months with 0.1% tacrolimus ointment showed good efficacy concerning the prevention of flares, which was similar to class III TCS.[71–73] The proactive treatment was associated with a reduction of the number of flares and an improvement of the quality of life both in adults and in children.[74,75] Pimecrolimus cream was studied in infants and children in combination treatment with TCS,[76,77] with TCS applied when a flare occurred. Data on pimecrolimus are also available for children younger than 2 years.[78,79]

Dosage: acute flare, short-term treatment, long-term treatment

The anti-inflammatory effect of 0.1% tacrolimus ointment is comparable with that of a class II–III glucocorticosteroid,[71,72,80], while 0.1% tacrolimus ointment is more effective than 0.03% tacrolimus ointment or 1% pimecrolimus cream.[73]

Safety

Safety data on both TCI have been obtained in numerous clinical studies and registries, and high-quality long-term safety data based on studies covering 10 years with tacrolimus and 5 years with pimecrolimus have been published, demonstrating the safety of this anti-inflammatory therapy in daily practice.[81,82]

TCI do not induce skin atrophy.[83,84] Accordingly, they are superior to TCS with respect to the use on sensitive body areas, such as eyelids, perioral skin, genital region, axillary region, or inguinal fold, and suitable for long-term treatment. Moreover, treatment with TCI may alleviate some side effects of TCS when applied to sensitive areas.[85]

For additional aspects of this chapter, see long version.

Future topical therapies *(only background text without recommendations; see long version)*

Antimicrobial therapy

Antibacterial therapy

In patients with AD with extensive superinfected lesions, therapy with systemic antibiotics *shall* be performed.	↑↑	100% consensus-based
Topical antibiotics *shall not* be used in AD, given the risk of resistance development and sensitization.	↓↓	100% consensus-based

For background text, see long version.

Antiviral therapy

Eczema herpeticum *shall* be treated immediately with systemic antiviral therapy.	↑↑	100% consensus-based

For background text, see long version.

Antifungal therapy

Topical or systemic antifungal therapy *should* be performed in patients with AD, especially with the "*head and neck*" variant of AD.	↑	100% consensus-based

For background text, see long version.

ANTIPRURITIC THERAPY

For antipruritic treatment, anti-inflammatory and systemic treatments *shall* be used according to the needs.	↑↑	> 75% consensus-based
The additional use of polidocanol for the treatment of pruritus in AD *may be considered*.	0	100% consensus-based
Topical antihistamines *shall not* be used for the treatment of pruritus in AD.	↓↓	100% consensus-based
Therapy with ultraviolet (UV) light (both narrowband UVB and UVA1) *should* be used temporarily for the treatment of pruritus in AD especially in adults and should also be considered for manifestations with limited inflammation.	↑	> 75% consensus-based
Systemic antihistamines of the first or second generation *shall not* be used as long-term treatment of pruritus in AD.	↓↓	100% consensus-based

Additional treatment with topical antiseptics *should* be performed in patients with AD with evident superinfection.	↑	100% consensus-based

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Selective serotonin reuptake inhibitors *should not* be used for the treatment of pruritus in AD.	↓	100% consensus-based
In adult patients with AD with depression or anxiety disorders, the use of selective serotonin reuptake inhibitors *may be considered* as second- or third-line therapy of chronic pruritus.	0	

For background text, see long version.

NON-PHARMACOLOGICAL THERAPY

Phototherapy and photochemotherapy

Narrowband UVB and medium doses of UVA1 *should* be used in adults with moderate to severe AD with a maximum of two therapeutic cycles a year.	↑	> 75% consensus-based
The use of narrowband UVB or UVA1 *may be considered* in *children or adolescents* after evaluation of the skin type (see background text). Frequent or long treatment cycles should be avoided.	0	> 75% consensus-based
Other modalities of phototherapy (UVAB, BB-UVB, UVA) *should* only be considered as second choice.	↑	> 75% consensus-based
Balneo phototherapy *may be considered* in adults with moderate to severe AD.	0	> 75% consensus-based
PUVA therapy (psoralen plus UVA) *may be considered*, if previous treatment cycles with other phototherapies were ineffective, while at the same time approved drug therapies are contraindicated or ineffective or have caused side effects.	0	100% consensus-based
During phototherapy, concomitant treatment with topical emollients *should* be performed.	↑	100% consensus-based
In patients with AD with a history of skin cancer or with an enhanced risk of skin cancer (including photodamaged skin) and in patients receiving systemic immunosuppressants, usually phototherapy *shall not* be performed.	↓↓	> 75% consensus-based

For background text, see long version.

Psychoeducative, psychosocial, and psychotherapeutic measures

Psychoeducative programs with verified effectiveness *shall* be used in children, adolescents, and adults with AD according to the needs.	↑↑	100% consensus-based
Participation in a structured interdisciplinary training course for legal custodians with children in the age group up to 7 years and for children (8–12 years) with AD and their legal custodians, and for patients ≥ 13 years of age *shall* be recommended according to the curriculum of the *Arbeitsgemeinschaft Neurodermitisschulung* (AGNES) and for adults according to the curriculum of the *Arbeitsgemeinschaft Neurodermitisschulung für Erwachsene* (ARNE) with chronic or chronic recurrent AD.	↑↑	100% consensus-based
Information about psychotherapeutic measures for disease management *should* be provided.	↑	100% consensus-based
If psychological comorbidity is suspected or evident, guideline-directed diagnosis and, if necessary, treatment *shall* be initiated according to the psychopathological diagnosis.	↑↑	100% consensus-based

For background text, see long version.

Food allergies and dietary interventions in AD

Individual dietary provocation factors *shall* be identified in moderate to severe AD in order to avoid these factors with the aim of prolonged remission or *clearance*.	↑↑	> 75% consensus-based

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IgE-mediated food allergy (immediate reaction): In patients with AD with a history of *food-induced immediate symptoms*, diagnostic methods for the assessment of IgE-mediated food allergy (food-specific IgE and/or skin prick test [SPT], diagnostic elimination diets, and provocation tests) *shall* be performed.	↑↑	> 75% consensus-based
IgE-mediated food allergy (immediate reaction) plus food-induced AD, delayed hypersensitivity: In patients with AD with a history of *food-related symptoms, including aggravation of AD*, diagnostic methods for the assessment of combined reactions to food products (immediate reaction plus food-related eczema) (food-specific IgE and/or SPT, diagnostic elimination diets, and provocation tests) *shall* be used.	↑↑	
History or suspicion of food-induced AD, delayed hypersensitivity: In patients with moderate to severe AD and *history or suspicion of AD triggered by food products*, diagnostic methods for the assessment of food products as provocation factors of AD (food-specific IgE and/or SPT, elimination diets, and provocation tests) *should* be performed.	↑	
In case of clinically relevant food allergy with verified diagnosis, a therapeutic elimination diet *shall* be performed in patients with AD.	↑↑	100% consensus-based
Dependent on history, diagnosis, and the triggering food product, re-evaluation of the IgE-mediated food allergy *shall* be performed in children.	↑↑	> 75% consensus-based
General dietary measures (such as, dietary supplements, general avoidance of certain food products like cow's milk, gluten) *shall not* be used in AD.	↓↓	100% consensus-based
In case of a food allergy, counselling by a nutritional expert trained in allergology *shall* be performed in order to ensure a balanced diet with therapeutic elimination diet and to avoid dietary errors.	↑↑	> 75% consensus-based
Vitamins *shall not* be used for the management of AD.	↓↓	> 75% consensus-based

For background text, see long version.

Allergen-specific immunotherapy (AIT)

If AIT is indicated due to inhalation allergy, AIT shall also be performed in case of concomitant AD.	↑↑	100% consensus-based

For background text, see long version.

Complementary medicine

Acupuncture *shall not* be used for the therapy of AD.	↓↓	> 75% consensus-based
Phytotherapy *shall not* be used for the therapy of AD.	↓↓	> 75% consensus-based
Autologous serum *shall not* be used for the therapy of AD.	↓↓	100% consensus-based
Chinese herbal medicine *shall not* be used for the therapy of AD.	↓↓	> 75% consensus-based

For background text, see long version.

Specific perspectives and situations

Perspective of patients

Patients with AD *shall* be treated in a holistic way; apart from the affected skin itself, the distress caused by the skin disease *shall* be considered.	↑↑	> 75% consensus-based
During the management of AD, lifestyle, preferences, and beliefs of the patients in relation to their disease *shall* be considered.	↑↑	> 75% consensus-based
Patients with AD with non-dermatological comorbidity *shall* be treated in an interdisciplinary manner.	↑↑	> 75% consensus-based
Treating physicians *shall* spend sufficient time to educate patients and their caregivers in the treatment and management of AD in a language easy to understand for laypersons.	↑↑	> 75% consensus-based
Patients with AD or caregivers *shall* receive knowledge, skills, resources, and support to enable the independent treatment of the disease at home and to manage its impact on their life.	↑↑	> 75% consensus-based

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For background text, see long version.

Pregnancy, lactation, family planning

Pregnancy

In women with AD, class II or class III TCS *shall* be used during pregnancy.	↑↑	100% consensus-based
In women with AD, TCI *shall* be used preferably in sensitive areas during pregnancy.	↑↑	100% consensus-based
In pregnant women with AD with inadequate topical therapies, UV therapy with narrowband UVB (311 nm) or UVA1, or, if these are not available, broadband UVB *shall* be used.	↑↑	> 75% consensus-based
In pregnant women with AD suitable for systemic treatment, the use of ciclosporin *should* be considered (off-label).	↑	100% consensus-based
In pregnant women with AD, long-term therapy with systemic glucocorticosteroids *shall not* be performed – this applies equally to all patients with AD.	↓↓	100% consensus-based
Janus kinase (JAK) inhibitors, methotrexate, and mycophenolate mofetil *shall not* be used during pregnancy.	↓↓	100% consensus-based
Given the lack of experience, dupilumab and tralokinumab *shall not* be used during pregnancy.	↓↓	100% consensus-based

For background text, see long version.

Lactation

In lactating women with AD, class II or class III TCS *shall* be used.	↑↑	100% consensus-based
In lactating women with AD, preferably TCI *shall* be used in sensitive areas.	↑↑	
In lactating women with AD, prednisolone *should be considered* only as short-term *rescue* therapy during acute flares.	↑	100% consensus-based
In lactating women with AD, methotrexate, JAK inhibitors, mycophenolate mofetil or azathioprine *should not* be used.	↓	100% consensus-based
Given the absence of clinical data, dupilumab or tralokinumab *should not* be used in lactating women with AD.	↓	100% consensus-based

For background text, see long version.
Family planning *see long version.*

Specific information for the treatment of children and adolescents

Important phenotypic and diagnostic differences

Eczemas can develop already in the first months of life, although manifestation of AD in the first 2 months of life is rare. More than 80% of patients with AD develop the disease before the fifth year of life. In the German *Multicenter Atopy Study* (MAS), a cumulative prevalence of AD of almost 22% in the first two years of life was found in a large birth cohort (n = 1,314). In approximately 43% of these patients, complete remission was observed after completion of the second year of life. In the German cross-sectional survey on allergic diseases in children and adolescents (KIGGS Wave 2), AD was medically diagnosed with a prevalence of 12.8% and thus more common than hay fever and asthma.[86]

A severe disease in early infancy and a family history of AD may be predictive parameters for a longer lasting disease course.[87] Especially in young infants with presumed refractory AD, additional differential diagnoses should be considered and the patients should be presented to pediatricians.

In infancy (age of 4 weeks to 12 months), AD is developing especially on cheeks, head, trunk, and the extensor sides of the extremities, although the flexor side may often be affected as well, which will be even more noticeable in later childhood.

The first clinical signs often arise on the cheeks in the form of erythematous, oozing, crusted plaques. Subsequently, the symptoms may appear in generalized form and extend to scalp, forehead, trunk, and extremities. In the facial region, the center of the face, especially the perinasal area, is free of inflammatory erythemas. In infants, manifestation of AD in the diaper area is usually mild or absent, in contrast to peers with seborrheic eczema that regularly exhibit involvement of the diaper area. Mostly, the facial symptoms decrease until the end of the first year of life.[88]

Infants are more susceptible to percutaneous toxicity. Given the unfavorable ratio of body surface to body mass, the still immature drug metabolism, and the smaller subcutaneous fat depots, the absorption potential of the skin increases while the distribution volume of an active ingredient or toxin is decreased. In infants born at full term, the development of the skin barrier continues during the first year of life.

Bathing of an infant has an important psychological benefit for the bond between parents and child. In infants with AD, bathing time should be kept short, for example, to maintain the microbial flora of the skin and to avoid maceration. Alkaline soaps and detergents should be avoided and emollients should be used as substitute for bath additives and soap in order to support skin hydration and barrier function.[89] The water temperature should not be too high.[90] Given that daily bathing or showering is not

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necessarily accompanied by an increase in disease severity, patients with AD should not be discouraged to take a bath or shower.[91]

Prevention

In children with AD, it is recommended to pay special attention to accompanying allergic diseases. Approximately one third of the patients with moderate to severe AD may develop food allergies in context of the skin barrier impairment; moreover, asthma and allergic rhinitis occur significantly more often compared to patients without AD. Based on the available evidence, currently no recommendation can be given for daily lipid replenishment of healthy skin of infants with the aim of primary prevention of eczemas and allergies – even in families with enhanced risk of allergy (see also Chapter "Basic therapy with emollients and moisturizers"). Regular visits to swimming pools to prevent AD should not be discouraged. There is no evidence for a preventive effect of dietary restriction by avoidance of potent food allergens in the first year of life. Furthermore, cohort studies could[92–94] show that diverse complementary food is accompanied with a reduced development of AD. For prevention of peanut allergy, in infants with AD in families with regular peanut consumption, consideration may be given to the introduction of peanut products in an age-appropriate form during initiation of complementary feeding, with subsequent maintenance. In infants with moderate to severe AD, peanut allergy shall be excluded first. A detailed presentation of preventive medical aspects is available in the current AWMF S3 guideline "Allergy prevention".[95]

Education and rehabilitation measures are presented in previous sections. The implementation of AD therapy requires an interdisciplinary approach including the expertise of appropriately qualified nurses (Section "Perspective of patients").

Topical anti-inflammatory therapy

Similar to adults, a step therapy with TCS of different potency is recommended. TCS of low to moderate potency are generally sufficient for mild to moderate AD affecting face and neck. Given the enhanced risk of adverse drug reactions in these locations (for example, skin atrophy, perioral dermatitis) they should be used only for a short time (3 to maximally 5 days). TCS of moderate potency are used for moderate AD. Mometasone furoate 0.1% is the only TCS of high potency with adequate benefit-risk ratio used for severe AD in childhood. Products with moderate to high potency are only used for a limited time (usually, 7 to maximally 14 days) in case of acute exacerbations. In sensitive locations, such as axillary or inguinal regions, less potent TCS or TCI should be used. In children younger than 12 years, the application of TCS once daily is often sufficient. Adolescents and adults are usually instructed to apply a TCS one to two times a day for short intensive treatments and to stop or reduce the use after stabilization of the AD exacerbations. In infants and toddlers, the use of highly potent TCS should only be performed under supervision of pediatricians or dermatologists with sufficient experience in treating this age group.[33] Generally, very potent TCS (for example, clobetasol propionate) shall not be used in childhood and, in particular, in infants and toddlers with AD.

In case of mild disease activity, maintenance therapy with TCS two to three times a week (monthly dose in the mean range of 15 g in infants, 30 g in children, and up to 60–90 g in adolescents and adults, adjusted to the affected body surface) with adequate basic therapy has no adverse systemic or local effects.[87]

TCI can be used compliant to their approval from the age of 3 months (pimecrolimus 1% cream) or 2 years (tacrolimus 0.03% ointment) and 16 years (tacrolimus 0.1% ointment) as effective and safe anti-inflammatory agents for the treatment of AD, especially on sensitive skin regions (for example, in the face). Application twice daily on the affected areas is recommended during a flare-up while observing the FTU rule; in the context of a proactive treatment, they can be applied also on areas free of symptoms twice weekly.[87] (See also Section "Anti-inflammatory therapy".)

One FTU is sufficient to treat the face of a 3-month-old infant. A dose of 4 FTU is used to cover an entire leg of a 6-year-old child completely (see also Section "Basic therapy with emollients and moisturizers").

Systemic therapy in childhood and adolescence

See part 2 and long version of the guidelines.

Occupational aspects

Adolescents and adults with AD *shall* be informed about the increased risk of developing occupation-related (hand) eczema, about prophylactic skin protection, and about the avoidance of irritants/contact allergens.	↑↑	100% consensus-based
If hand eczema has already developed in adolescence in the context of AD, adoption of wet occupations *should not* be recommended.	↓	> 75% consensus-based
In advance of an occupation, an individual consultation about the choice of occupation, including risk assessment, avoidance strategies, and protection measures, *shall* be performed.	↑↑	100% consensus-based
Potential occupational trigger factors of AD *shall* be reduced. In the context of prevention, skin protection measures shall be implemented.	↑↑	100% consensus-based

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If occupation-related hand eczema with a course congruent to work is suspected, patients with AD *shall* be advised to initiate a dermatologist's procedure pursuant to § 3 BKV to make use of the secondary and tertiary prevention services provided by the German statutory accident insurance.	↑↑	> 75% consensus-based

For background text, see long version.

AFFILIATIONS

[1]Department of Dermatology, Allergology and Venereology, Hannover Medical School, Hannover, Germany

[2]Department of Dermatology and Venereology, Medical University of Graz, Graz, Austria

[3]Competence Center for Health Services Research in Dermatology (CVderm), Institute for Health Services Research in Dermatology and Nursing (IVDP), University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[4]Department of Dermatology and Allergology, University Medical Center, Technical University of Munich, Munich, Germany

[5]Department of Dermatology, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany

[6]Department of Dermatology, Venereology and Allergology, University Hospital Schleswig-Holstein, Campus Kiel, Germany

[7]German Allergy and Asthma Association (DAAB), Mönchengladbach, Germany

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

[9]Office for Pediatric Pneumology and Allergology, Pediatric Center Dresden-Friedrichstadt (Kid), Dresden, Germany

[10]Hospital Hallerwiese, Cnopfsche Kinderklinik, Nuremberg, Germany

[11]Department of Psychosomatic Medicine and Psychotherapy, University Hospital Gießen, Gießen, Germany

[12]Dermatology Office, Selters, Germany

[13]Allergy Unit, Department of Dermatology, University Hospital Zurich, Zurich, Switzerland

[14]Center for Evidence-Based Healthcare (ZEGV), Medical Faculty Gustav Carus, Technical University Dresden, Dresden, Germany

[15]German Eczema Association (DNB), Hamburg, Germany

[16]Department of Dermatology, Inselspital Bern, Bern, Switzerland

[17]Specialized Clinic for Pediatric Pneumology and Allergology, Wangen, Germany

[18]Institute of Environmental Medicine, University Hospital Augsburg, Augsburg, Germany

[19]Department of Dermatology and Allergology, University Hospital Augsburg, Augsburg, Germany

[20]Department of Dermatology and Allergy, Ludwig Maximilian University Munich, Munich, Germany

[21]Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

[22]Department of Pediatric Dermatology and Allergology, Children's and Adolescents' Hospital Auf der Bult, Hannover, Germany

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CONFLICT OF INTEREST

A tabular listing of conflicts of interest of all parties involved can be found in the long version of the guideline.

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