Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V (keine Stellungnahmen eingegangen)

Vorgang: 2023-B-176 Delgocitinib

Stand: Juli 2023

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Delgocitinib
[mittelschweres bis schweres chronisches Handekzem]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	− NB-UVB − UVA (die UVA1 ist hiervon ausgenommen, da ausgeschlossen)
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Delgocitinib	Geplantes Anwendungsgebiet laut Beratungsanforderung: Behandlung erwachsener Patienten mit mittelschwerem bis schwerem chronischen Handekzem (CHE), die auf topische Kortikosteroide unzureichend angesprochen haben oder für die eine Behandlung mit topischen Kortikosteroiden nicht angezeigt ist.
Alitretinoin ATC: D11AH04 z.B. Toctino Weichkapseln®	Toctino ist angezeigt bei Erwachsenen mit schwerem chronischen Handekzem, das auf die Behandlung mit potenten topischen Kortikosteroiden nicht anspricht. Patienten, bei denen das Ekzem überwiegend hyperkeratotische Eigenschaften hat, reagieren in der Regel besser auf die Behandlung als Patienten, deren Ekzem in Form eines Pompholyx auftritt.

Quellen: AMIce-Datenbank, Fachinformation

Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Aufgrund von Überschneidungen in der Therapie hier zusätzlich aufgeführt: Behandlung der atopischen Dermatitis	
Hinweis	***Aufgrund der großen Menge an Wirkstoffen im Anwendungsgebiet werden hier einzelne Arzneimittel exemplarisch aufgeführt***
TOPISCHE THERAPIEN	
Glukokortikoide Klasse 1:	
Prednisolon D07AA03 z.B. Prednisolon Creme LAW	Zur Behandlung subakuter und akuter gering ausgeprägter entzündlicher Hauterkrankungen, die auf eine äußerliche Behandlung mit schwach wirksamen Corticosteroiden ansprechen.
Hydrocortison D07AA02 z.B. Hydrocortison Heumann 1 % Creme	Zur Behandlung von entzündlichen Hauterkrankungen, bei denen schwach wirksame, topisch anzuwendende Glucocorticosteroide angezeigt sind.
Glukokortikoide Klasse 2:	
Hydrocortison-17-butyrat D07AB02 z.B. Laticort® Creme 0,1 %	Zur Behandlung entzündlicher Hautkrankheiten, bei denen mittelstark wirksame, topisch anzuwendende Glucocorticoide angezeigt sind. Creme: insbesondere bei akuten und subakuten Formen, in intertriginösen Arealen und beim fettigen Hauttyp. Salbe: insbesondere bei subakuten bis chronischen Formen.
Clobetasonbutyrat 0,5 mg D07AB01 z.B. Emovate® Creme	Leichte Formen von Ekzemen, seborrhoischer Dermatitis und andere leichte Hauterkrankungen, die auf eine lokale Corticoidbehandlung ansprechen. Weiterbehandlung von hartnackigen Hauterkrankungen, die mit einem starker wirkenden Corticoid anbehandelt worden sind. Bei Säuglingen und Kleinkindern zur lokalen Corticoidbehandlung, z. B. Windelekzem oder endogenem Ekzem.

Triamcinolon-acetonid D07AB09 z.B. AbZ Salbe 0,1 %	Zur Behandlung entzündlicher Hautkrankheiten, bei denen mittelstark wirksame topisch anzuwendende Glukokortikoide angezeigt sind. Triamcinolon AbZ 0,1 % Creme eignet sich insbesondere für akute bis subchronische sowie nässende Dermatosen ohne keratotische Veränderungen.
Glukokortikoide Klasse 3:	
Prednicarbat D07AC18 z.B. Prednicarbat acis® Creme	Entzündliche Hauterkrankungen, bei denen eine äußerliche Behandlung mit mittelstark wirksamen Glucocorticoiden angezeigt ist, wie z. B. mäßig stark ausgeprägtes Ekzem.
Methylprednisolon-aceponat D07AC 14 Advantan® 0,1 % Creme	Zur Behandlung des endogenen Ekzems (atopische Dermatitis, Neurodermitis), Kontaktekzems, degenerativen Ekzems und des nummulären Ekzems.
Amcinonid D07AC11 z.B. Amciderm® Fettsalbe	Hauterkrankungen, die auf stark wirksame Kortikoide ansprechen wie z.B. toxische Ekzeme, allergische Kontaktekzeme, atopisches Ekzem (Neurodermitis), Psoriasis vulgaris, Lichen ruber.
Mometasonfuroat D07AC13 z.B. ECURAL® Fettcreme, 1 mg/g Creme	Fettcreme und Salbe sind angezeigt zur Behandlung aller entzündlichen und juckenden Hauterkrankungen, die auf eine äußere Behandlung mit Glukokortikoiden ansprechen wie Psoriasis, atopische Dermatitis und Reiz- und/oder allergische Kontaktdermatitis.
Glukokortikoide Klasse 4:	
Clobetasol-propionat D07AD01 z.B. Clobetasol acis® Creme, 0,5 mg/g	Zur Behandlung lokalisierter therapieresistenter Plaques von entzündlichen Hauterkrankungen bei denen die symptomatische Anwendung topischer Glukokortikoide mit sehr starker Wirkung angezeigt ist.

Calcineurinhemmer	
Tacrolimus D11AH01 Protopic® 0.03% Salbe	Behandlung des mittelschweren bis schweren atopischen Ekzems bei Kindern ab 2 Jahren, die nicht ausreichend auf eine herkömmliche Therapie wie z. B. topische Kortikosteroide angesprochen haben. Als Erhaltungstherapie.
Pimecrolimus D11AH02 Elidel® 10 mg/g Creme	Behandlung von Patienten ab einem Alter von 3 Monaten mit leichtem oder mittelschwerem atopischem Ekzem, wenn eine Behandlung mit topischen Kortikosteroiden entweder nicht angebracht oder nicht möglich ist, wie z. B. bei: Unverträglichkeit gegenüber topischen Kortikosteroiden; mangelnder Wirksamkeit von topischen Kortikosteroiden; Anwendung im Gesicht und Halsbereich, wo eine intermittierende Langzeitbehandlung mit topischen Kortikosteroiden nicht empfehlenswert ist.
SYSTEMISCHE THERAPIEN	
Dupilumab D11AH05 Dupixent®	*Erwachsene und Jugendliche* Dupixent wird angewendet zur Behandlung von mittelschwerer bis schwerer atopischer Dermatitis (AD) bei Erwachsenen und Jugendlichen ab 12 Jahren, die für eine systemische Therapie in Betracht kommen. *Kinder von 6 Monaten bis 11 Jahre* Dupixent wird angewendet zur Behandlung von schwerer atopischer Dermatitis bei Kindern von 6 Monaten bis 11 Jahre, die für eine systemische Therapie in Betracht kommen.
Upadacitinib L04AA44 Rinvoq®	Rinvoq wird angewendet zur Behandlung der mittelschweren bis schweren atopischen Dermatitis bei Erwachsenen und Jugendlichen ab 12 Jahren, die für eine systemische Therapie infrage kommen.
Abrocitinib D11AH08 Cibinqo®	Cibinqo wird angewendet zur Behandlung von mittelschwerer bis schwerer atopischer Dermatitis bei Erwachsenen, die für eine systemische Therapie infrage kommen.
Baricitinib L04AA37 Olumiant®	Baricitinib wird angewendet zur Behandlung von mittelschwerer bis schwerer atopischer Dermatitis bei erwachsenen Patienten, die für eine systemische Therapie infrage kommen.
Tralokinumab D11AH07 Adtralza®	Adtralza wird angewendet zur Behandlung mittelschwerer bis schwerer atopischer Dermatitis bei Erwachsenen und Jugendlichen ab 12 Jahren, die für eine systemische Therapie in Frage kommen.
Ciclosporin L04AD01	Ciclosporin dura ist indiziert bei Patienten mit schwerer atopischer Dermatitis, falls eine systemische Therapie erforderlich ist.

z.B. Ciclosporin dura®	
Systemische Glucokortikoide	
Methylprednisolon H02AB04 Methylprednisolon JENAPHARM®	Erkrankungen, die einer systemischen Therapie mit Glucocorticoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad zum Beispiel: Erkrankungen der Haut und Schleimhäute, die aufgrund ihres Schweregrades und/oder Ausdehnung bzw. Systembeteiligung nicht oder nicht ausreichend mit topischen Glucocorticoiden behandelt werden können.
Triamcinolon H02AB08 Volon® 4, 8, 12 mg Tabletten	Orale Anfangsbehandlung ausgedehnter, schwerer akuter, auf Glukokortikoide ansprechender Hautkrankheiten wie: Allergische Dermatosen (z. B. akute Urtikaria, Kontaktdermatitis, Arzneimittelexanthem), atopisches Ekzem (akute Exazerbationen bzw. großflächige nässende Ekzeme), Pemphigus vulgaris.
Antihistaminika	
z.B.Cetirizin-dihydrochlorid R06A E07 Cetirizin beta® Filmtablette	Zur Behandlung von Krankheitssymptomen bei allergischen Erkrankungen wie – Juckreiz bei chronischer Nesselsucht (Urtikaria) und bei atopischer Dermatitis (Neurodermitis) mit Beschwerden wie Rötung der Haut

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2023-B-176 (Delgocitinib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	11. Juli 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Atopic eczema
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
AZA	Azathioprine
Bari	Baricitinib
CHE	Chronic hand eczema
CyA	Ciclosporin
Dupi	Dupilumab
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HE	Hand eczema
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
MTX	Methotrexate
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
Tralo	Tralokinumab
TRIP	Turn Research into Practice Database
Upa	Upadacitinib
UVA1	Ultraviolet A1;
NB-UVB	Narrow-band ultraviolet B
WHO	World Health Organization

1 Indikation

Behandlung erwachsener Patienten mit mittelschwerem bis schwerem chronischen Handekzem (CHE), die auf topische Kortikosteroide unzureichend angesprochen haben oder für die eine Behandlung mit topischen Kortikosteroiden nicht angezeigt ist.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Handekzem durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.google.com/) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 02.03.2021 durchgeführt, die folgenden am 19.11.2021 und 28.06.2023. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 605 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 5 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Es wurden keine relevanten Systematischen Reviews identifiziert.

3.3 Leitlinien

Thyssen JP et al., 2022 [3].

Guidelines for diagnosis, prevention, and treatment of hand eczema

Zielsetzung/Fragestellung

To update the European Society of Contact Dermatitis guideline on the diagnosis, prevention, and treatment on of hand eczema

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger Evidenz im AWG, wird die Leitlinie ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz: basiert auf 2 CR und zusätzlicher Suche;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: The guidelines are expected to be valid until 2025, at the latest.

Recherche/Suchzeitraum:

- CR on interventions for hand eczema (HE): Christoffers WA, Coenraads P-J, Svensson Å, et al. Interventions for hand eczema. Cochrane Database Syst Rev. 2019;4:CD004055.
- CR on interventions for the primary prevention of occupational irritant hand dermatitis Bauer A, Schmitt J, Bennett C, et al. Interventions for preventing occupational irritant hand dermatitis. Cochrane Database Syst Rev. 2010;6:CD004414.
- searches were updated up to April 2020

LoE

TABLE 1 Assessment of the strength of evidence

Syntax	Quality/ certainty of evidence
We are very confident that the true effect lies close to that of the estimate of the effect	High
We are moderately confident in the effect estimate	Moderate
Our confidence in the effect is limited; we have very little confidence in the effect estimate	Low and very low

GoR

TABLE 2 Grades of recommendation

Syntax	Grade of recommendation	Symbol
'We recommend', 'we do not recommend'	Strong	A
'We suggest', we do not suggest'	Weak	B
'May be considered'	Open	0

Empfehlungen

8.Treatment

TABLE 8 Treatment recommendations for hand eczema (HE)

	Standard therapy	Almost clear HE	Moderate HE	Severe or very severe HE
Recommend	Educational programs and instructions Emollients Protective gloves Avoidance of clinically relevant allergens	Moderate topical corticosteroids	Moderate and potent topical corticosteroids	Moderate and potent topical corticosteroids Alitretinoin
Suggest		Tacrolimus ointment	Phototherapy Tacrolimus ointment	Cyclosporine A[a]
May be considered				Methotrexate[b] Azathioprine[b] Acitretin[b], in hyperkeratotic hand eczema

Note: Severity is based on the photographic guide.[209]
[a]Off-label systemic treatment, except for atopic hand eczema in some countries.
[b]Off-label systemic treatment for hand eczema.

8.1 General principles of treatment

- We recommend identification and avoidance of causative exogenous factors. Consensus-based recommendation (first round 100% [12/12], second round 100% [22/22]).

8.2 Topical treatments

8.2.1 Emollients and moisturizers

- We recommend that emollients/moisturizers are frequently used in all HE patients. Consensus-based recommendation (first round 100% [8/8], second round 100% [21/21]).
- We recommend that the choice of emollient should be individualized according to skin condition, patients' preference, and existing (contact) allergies. Consensus-based recommendation (first round 100% [12/12], second round 100% [22/22]).

8.2.3 Topical calcineurin inhibitors

- We suggest tacrolimus ointment for short-term treatment in the management of HE. Quality of evidence: moderate. Grade of recommendation: B.
- We suggest using tacrolimus ointment for HE patients either refractory to topical corticosteroid or when fear of side effects of topical corticosteroid exist, or in the chronic stage. Consensusbased recommendation (first round 92% [11/12], second round 91% [21/23]). Doctors and patients need to be aware that this is an off-label treatment, except for patients with atopic HE.

Hintergrund:
The topical calcineurin inhibitors tacrolimus and pimecrolimus are registered for the treatment of AD, not for HE of other aetiologies. The 2019 Cochrane review on HE included four small studies on tacrolimus (107 participants in total) and five larger studies on pimecrolimus (1059 participants), all of rather short duration (≤8 weeks).1 Tacrolimus 0.1% ointment probably improves investigator-rated symptom control measured after 3 weeks compared to vehicle (14/14 tacrolimus vs 0/14 vehicle).162[…] The evidence was assessed as moderate certainty, based on GRADE.
Data for pimecrolimus 1% are conflicting and were not assessed with GRADE in the Cochrane review of 2019. Overall, no significant difference in efficacy was found between pimecrolimus and placebo. The skin barrier on the palms is fundamentally different from the dorsal aspects of the hands. Thus, the large calcineurin inhibitor molecules may more easily penetrate the dorsal aspects, in part resulting in better chance of efficacy

8.3 Physical therapies

8.3.1 Phototherapy

- We suggest phototherapy of the hands in adult patients with CHE refractory to topical corticosteroids. Quality of evidence: moderate. Grade of recommendation: B. Consensus-based recommendation (first round 100% [12/12], second round 100% [22/22]).
- Long-term use of phototherapy may increase the risk of skin malignancy. Consensus-based statement (only one round: 100% [22/22]).

Hintergrund:
Ten studies on UV-therapy were included in the Cochrane systematic review.1 There was too much heterogeneity regarding interventions, comparators, and outcomes to perform a meta-analysis. Of these 10, one comparative study was assessed with GRADE: narrow-band-UVB vs psoralen-UVA (PUVA).163 This study showed that there is probably little to no difference in efficacy, but that PUVA may result in more adverse events (9/30 vs 0/30) (both moderate certainty evidence). Oral as well as bath, paint, or cream PUVA are used in some countries164,165 and seem to be similarly effective. UVA1 may also be effective,166,167 but availability is often limited.
Adverse events of phototherapy, especially local PUVA, are erythema and burning of the skin, and long-term use increases the risk of (non-melanoma) skin cancer.168 Grenz ray treatment was used in the past but is considered obsolete because pf a possible increased risk of skin cancer.169–174

8.4 Systemic treatment

- We recommend alitretinoin as a second-line treatment (relative to topical treatment) for patients with severe chronic hand eczema (CHE). Quality of evidence: high. Grade of

recommendation: A. Consensus-based recommendation (first round 100% [12/12], second round 100% [22/22]).

- We suggest short-term oral corticosteroids to be used only in acute and severe inflammation as part of a treatment plan, for example, when starting systemic treatment with a slower onset of effect. Consensus-based recommendation (first round 100%, [12/12], second round 100% [22/22]).
- We suggest cyclosporine for CHE patients refractory or contraindicated to first- and second-line therapy. Consensus-based recommendation. Doctors and patients need to be aware that this is an off-label treatment, except for patients with atopic HE. Consensus-based recommendation (first round 100% [12/12], second round 100% [22/22]).
- Azathioprine may be considered for CHE patients refractory or contra-indicated to first- and second-line therapy, although evidence for its efficacy is limited. Consensus-based recommendation. Doctors and patients need to be aware that this is an off-label treatment. Consensus-based recommendation (first round 100% [12/12], second round 100% [23/23]).
- Methotrexate may be considered for CHE patients refractory or contra-indicated for first- and second-line therapy, although evidence for its efficacy is limited. Consensus-based recommendation. Doctors and patients need to be aware that this is an off-label treatment. Consensus-based recommendation (first round 100% [12/12], second round 100% [23/23]).
- Acitretin may be considered for hyperkeratotic CHE, if other therapeutic options are unavailable or contra-indicated, although evidence for its efficacy is limited Consensus-based recommendation. Doctors and patients need to be aware that this is an off-label treatment. Consensus-based recommendation (first round 100% [12/12], second round 100% [23/23]).

Hintergrund:
Except for alitretinoin, no other systemic treatments are licensed for the treatment of CHE.
Alitretinoin
The oral vitamin-A derivative (retinoid) alitretinoin is registered for use of treating severe CHE that inadequately responds to treatment with (very) potent topical corticosteroids. Four studies with alitretinoin vs placebo were included in the Cochrane review.1 These studies entailed dosages of 10 mg and 30 mg vs placebo and were as such assessed with GRADE. Two RCTs (n = 1210) in people with severe CHE that was refractory to standard treatment, assessed the efficacy of alitretinoin 30 mg vs placebo (both arms could use emollients). The main outcomes were the proportion of participants who achieved good/excellent control of symptoms, defined as reaching clear or almost clear, both assessed by investigators and participants (investigator global assessment/ patient global assessment 0 or 1; scale 0-4). Investigators reported achieving good/excellent control of 44.4% on alitretinoin 30 mg and 15.7% on placebo. The participants reported 39.6% achieving good/ excellent control on alitretinoin 30 mg vs 14.3% on placebo. Two RCTs on 10 mg alitretinoin vs placebo (n = 781) used the same primary outcomes.
Here, investigators reported achieving good/excellent control of 29.3% on alitretinoin 10 mg and 19.4% on placebo. Participants reported 24.8% achieving good/excellent control on alitretinoin 10 mg vs 14.4% on placebo. The reported adverse events (including headache) did not differ between alitretinoin 10 mg and placebo, but the risk of headache increased with alitretinoin 30 mg. A limitation of these four studies might be that the characterization of the type of HE was not stratified, and thus could not show difference in efficacy between, for example, hyperkeratotic and vesicular HE. Post hoc it was shown that alitretinoin was probably more effective in hyperkeratotic types.175 This is reflected in the Summary of Product Characteristics (SmPC) of alitretinoin, which states that HE with predominantly hyperkeratotic features is more likely to respond than HE presenting as pompholyx.176
The most common adverse effect was headache,177 and alitretinoin is associated with an increase in plasma cholesterol and triglyceride levels, and a decrease in thyroid function parameters; these should be monitored during therapy.131 Its safety profile is consistent with other molecules from the retinoid class. Being a retinoid, alitretinoin is teratogenic and, therefore, pregnancy prevention measures are indicated during treatment, for which local guidelines should be followed.

Deutsche Dermatologische Gesellschaft (DDG), 2023 [1].

Diagnostik, Prävention und Therapie des Handekzems; S2k-Leitlinie, Langfassung

Zielsetzung/Fragestellung

Allgemeines Ziel der Leitlinie ist es, Dermatologen und Allergologen in der Praxis und Klinik eine akzeptierte, evidenzbasierte Entscheidungshilfe für die Auswahl sowie Durchführung einer geeigneten und suffizienten Therapie für Patient*innen mit Handekzemen zur Verfügung zu stellen.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger Evidenz im AWG, wird die Leitlinie ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft nicht zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: Gültigkeit bis zum 22.02.2028

Recherche/Suchzeitraum:

- Kapitel zu Therapieempfehlungen basiert auf Cochrane Review von Christoffers WA

Christoffers WA, Coenraads PJ, Svensson Å, et al. Interventions for hand eczema. Cochrane Database Syst Rev. 2019; 4: Cd004055.

LoE/GoR

- Entsprechend der gewählten Entwicklungsstufe erfolgte keine systematische Bewertung der Qualität der Evidenz.

Tabelle 10: Empfehlungsstärken – Wortwahl, Symbolik und Interpretation (modifiziert nach Kaminski-Hartenthaler et. al, 2014 [256])

Symbol	Bedeutung
↑↑	Starke Empfehlung: soll
↑	Empfehlung: sollte
0	Empfehlung offen
↓	Empfehlung: sollte nicht
↓↓	Starke Empfehlung: soll nicht
	Keine Empfehlung.

Empfehlungen

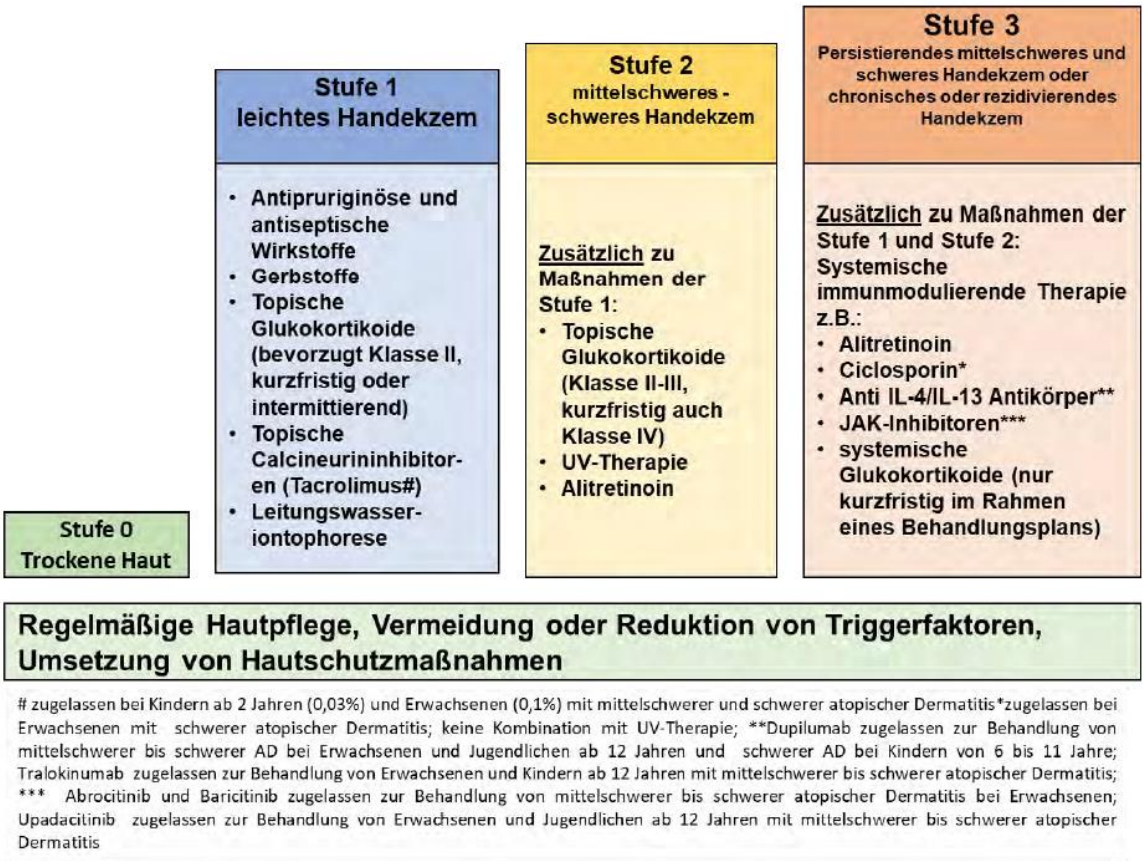


Abbildung 1: Stufenweise Therapie bei Handekzemen entsprechend des Schweregrades

Allgemeine Therapieprinzipien

Empfehlung	Stärke	Zustimmung
Ursächliche exogene Faktoren **sollen** identifiziert und vermieden werden.	↑↑	100% (10/10) Expertenkonsens

Topische Therapien

Basistherapeutika (Hautpflegemittel)

Empfehlung	Stärke	Zustimmung
Die regelmäßige Anwendung von Basistherapeutika (Hautpflegemitteln) **soll** bei allen HE-Patient*innen erfolgen.	↑↑	100% (12/12) Expertenkonsens

Hintergrund:

Die Leitlinien-Arbeitsgruppe empfiehlt ausdrücklich den Einsatz von Hautpflegemitteln zur Behandlung des HE, um die Hautbarrierefunktion zu erhalten und/oder zu verbessern. Wichtige Faktoren für die Wahl der Hautpflegemittel sind Präferenzen des/der Patient*in und bestehende (Kontakt-)Allergien. Zur Optimierung der Anwendung und der Adhärenz ist eine Unterweisung durch medizinische Fachkräfte sinnvoll (wann, wie, welches Produkt). In der Praxis werden bei hyperkeratotischem HE gelegentlich Hautpflegemittel mit 10% Harnstoff - oder andere Keratolytika - verwendet, aber es gibt keine wissenschaftlichen Belege, die eine derartige Empfehlung unterstützen.

Topische Calcineurin-Inhibitoren

Empfehlung	Stärke	Zustimmung
Tacrolimus*-Salbe (0,1%) **kann** für die Kurzzeittherapie bei der Behandlung von HE eingesetzt werden.	0	100% (11/11) Expertenkonsens
Zur Erhaltungstherapie **kann** eine proaktive Therapie mit Tacrolimus*-Salbe (0,1%) eingesetzt werden.	0	100% (12/12) Expertenkonsens

**off-label (sofern die Behandlung nicht bei „atopischem Handekzem" erfolgt)*

Hintergrund:
Die topischen Calcineurin-Inhibitoren Tacrolimus und Pimecrolimus sind für die Behandlung des atopischen HE zugelassen, nicht jedoch für HE anderer Ätiologien. Der Cochrane-Review von 2019 zu HE umfasste vier Studien mit begrenzten Fallzahlen zu Tacrolimus (insgesamt 107 Teilnehmer*innen) und fünf größere Studien zu Pimecrolimus (1059 Teilnehmer*innen), mit kurzer Dauer (≤ 8 Wochen). [195] Tacrolimus 0,1% Salbe verbessert laut ärztlichem Urteil die Symptomkontrolle, gemessen nach drei Wochen, im Vergleich zu Vehikel (14/14 Tacrolimus versus 0/14 Vehikel) [223]. Von den Teilnehmer*innen beurteilte Symptome wurden nicht gemessen. Brennen oder Juckempfindungen wurden bei 4/19 Personen in der Tacrolimus-Gruppe berichtet gegenüber 0/14 Personen in der Vehikelgruppe. Die Evidenzsicherheit wurde auf der Grundlage von GRADE als moderat bewertet. In einer Studie mit einem „Within-Participants-Design" mit 16 Patient*innen wurde Tacrolimus 0,1% Salbe mit Mometasonfuroat 0,1% Salbe verglichen, aber es wurden keine von den Prüfärzt*innen oder Teilnehmer*innen beurteilten Symptome berichtet [219]. Beide Therapien waren gut verträglich. Die Evidenzsicherheit wurde als moderat eingestuft.
Die Daten für Pimecrolimus 1% sind widersprüchlich und wurden im Cochrane-Review von 2019 nicht nach GRADE bewertet. Insgesamt wurden keine signifikanten Unterschiede in der Wirksamkeit zwischen Pimecrolimus und Placebo festgestellt. Die Hautbarriere auf der Handfläche unterscheidet sich grundlegend von der dorsalen Seite der Hand. Die großen Calcineurin-Inhibitor-Moleküle können möglicherweise auf der Dorsalseite der Hände besser in die Haut eindringen und daraus resultierend erhöhen sich die Chancen auf eine bessere Wirksamkeit.

Unterstützende Lokaltherapie

In der Praxis hat es sich bewährt in Abhängigkeit von der Morphe und dem Stadium der Erkrankung auch ergänzende topische Therapiemaßnahmen zu ergreifen (siehe Tabelle 7).

Tabelle 7: Basistherapie/unterstützende Lokaltherapie

Morphe	angenommene Wirkung	Basistherapie/unterstützende Lokaltherapie (Beispiele)
vesikulär, „dyshidrosiform“	austrocknend, adstringierend	• synthetische Gerbstoffe (tanninartig), • Lotio alba, Pasta exsiccans NRF, (fett-)feuchte Umschläge • bei Kombination mit Hyperhidrosis evtl. Aluminiumchloridhexahydrat, Leitungswasseriontophorese (s. AWMF-Leitlinie [224])
nässend/ superinfiziert	austrocknend, desinfizierend, antibakteriell	• Grundregeln der topischen Therapie: „feucht auf feucht“ • (fett-)feuchte Umschläge • Chlorhexidin, Polyhexanid, Octenidin, Clioquinol
Hyperkeratosen/ Rhagaden	keratolytisch, antiproliferativ	• salicylsäurehaltige Salben (≤10% auch unter Okklusion) • harnstoffhaltige Salben • Hydrokolloid-Verbände (Rhagaden) • Cignolin
subakute Ekzemreaktion/ Lichenifikation	antiinflammatorisch/ antipruriginös, rückfettend	• ichthyolhaltige Externa • Polidocanol (Macrogollaurylether), Harnstoff in Externa
trocken, schuppig	Rückfettung, Ekzemprophylaxe	• Grundregel der topischen Therapie: Rückfettung mit Öl-in-Wasser- oder Wasser-in-Öl-Emulsion • glycerinhaltige Basiscreme etc.

Physikalische Therapien

Phototherapie

Empfehlung	Stärke	Zustimmung
Bei erwachsenen Patient*innen mit moderat bis schwerem CHE, das therapierefraktär auf topische Glukokortikoide ist, **sollte** eine Phototherapie (topische PUVA, Schmalband-UVB, UVA1) der Hände erfolgen.	↑	100% (10/10) Expertenkonsens
Wegen der Assoziation langfristiger unerwünschter Wirkungen mit der kumulativen UV-Dosis **soll** die Phototherapie **nicht** für Langzeitbehandlungen verwendet werden.	↓↓	100% (11/11) Expertenkonsens

Systemtherapien

Empfehlung	Stärke	Zustimmung
Alitretinoin **soll** bei Patient*innen mit mittelschwerem bis schwerem CHE eingesetzt werden, wenn eine topische und/oder Phototherapie alleine nicht ausreichend wirksam sind.	↑↑	100% (11/11) Expertenkonsens
Ein oraler Glukokortikoidstoß **kann** in Einzelfällen bei akuten und schweren Entzündungen in Kombination mit anderen Therapeutika, als Teil eines Behandlungsplans z. B. zu Beginn einer systemischen Behandlung mit langsamerem Wirkungseintritt eingesetzt werden.	0	100% (10/10) Expertenkonsens
Ciclosporin* **sollte** bei Patient*innen mit mittelschwerem bis schwerem CHE eingesetzt werden, bei denen Refraktärität oder Kontraindikationen gegenüber der Erst- und Zweitlinientherapie bestehen.	↑	100% (10/10) Expertenkonsens
Azathioprin** **kann** bei Patient*innen mit mittelschwerem bis schwerem CHE, bei denen Refraktärität oder Kontraindikationen gegenüber der Erst- und Zweitlinientherapie bestehen, eingesetzt werden.	0	100% (10/10) Expertenkonsens
Methotrexat** **kann** bei Patient*innen mit mittelschwerem bis schwerem CHE, bei denen Refraktärität oder Kontraindikationen gegenüber der Erst- und Zweitlinientherapie bestehen, eingesetzt werden.	0	100% (10/10) Expertenkonsens
Acitretin** **kann** bei Patient*innen mit mittelschwerem bis schwerem CHE, bei denen andere Therapieoptionen nicht verfügbar oder kontraindiziert sind, eingesetzt werden.	0	100% (10/10) Expertenkonsens

**off-label (sofern die Behandlung nicht bei „atopischen Handekzem" erfolgt)*
*** off-label*

Mit Ausnahme von Alitretinoin sind keine weiteren Systemtherapien für die Behandlung von CHE zugelassen.

Wollenberg A et al., 2022 [2,4,5].

European guideline (EuroGuiDerm) on atopic eczema: part I & part II

Zielsetzung/Fragestellung

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

- 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.

Part two of the guideline will address avoidance of provocation factors, dietary interventions, immunotherapy, complementary medicine, educational interventions, occupational and psychodermatological aspects, patient perspective and considerations for paediatric, adolescent, pregnant and breastfeeding patients.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger Evidenz , wird die Leitlinie ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium; trifft zu.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt; trifft zu.
- Systematische Suche, Auswahl und Bewertung der Evidenz; living systematic review by Drucker et al. was used.
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt; trifft zu.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; trifft zu.
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- living systematic review by Drucker et al. was used.; last update 2022

Drucker AM, Morra DE, Prieto-Merino D, Ellis AG, Yiu ZZN, Rochwerg B, et al. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis. JAMA Dermatol. 2022;158; 523-532.

LoE

- Cochrane Risk of Bias tool

GoR

Table 3 Recommendation strengths – wording, symbols and interpretation and definition of certainty of evidence[6]

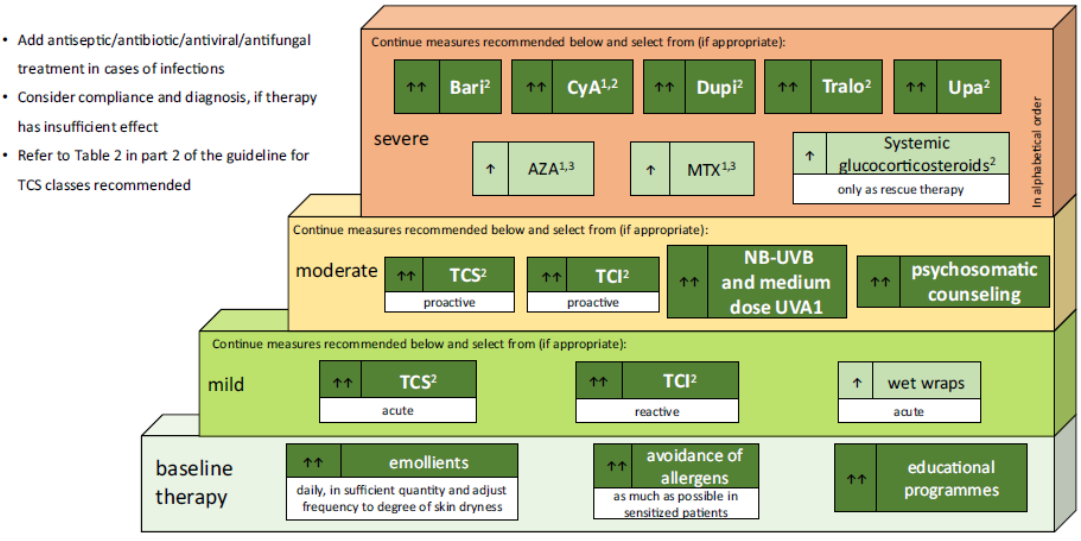
Strength	Wording	Symbols	Implications
Strong recommendation **for** the use of an intervention	'**We recommend . . .**'	↑↑	We believe that all or almost all informed people would make this choice.
Weak recommendation **for** the use of an intervention	'**We suggest . . .**'	↑	We believe that most informed people would make this 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 of or against an intervention cannot be made due to certain reasons (e.g. no reliable evidence available, conflicting outcomes)
Weak recommendation **against** the use of an intervention	'**We suggest against . . .**'	↓	We believe that most informed people would make a choice against this 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 this intervention.
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.			

TABLE 7: STRENGTH OF CONSENSUS

100 % consensus	100% agreement	
Strong consensus	Agreement of >95% - < 100% participants	
Consensus	Agreement of >75-95% participants	
Agreement of the majority	Agreement of >50-75% participants	

Empfehlungen:

Stepped-care plan for adults with atopic eczema



[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

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.

Figure 1 Stepped-care plan for adults with AE.

Table 4 General recommendations for systemic drugs in adult AE 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	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: 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 licence for adults and children; 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
Time to relapse (weeks, based on expert experience)[2]	<2	>12	>12	>8	>8	<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	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; 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

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.

[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

Conventional systemic drugs

Azathioprine (AZA)

We **suggest** using azathioprine in AE patients who are candidates for systemic treatment.	↑	>75%  (15/16) 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 main analysis) ⊗⊗○○ LOW for mean difference / standardized mean difference **change in signs**, DLQI, Itch VAS; OR undesirable effects Short term (8-16 weeks) vs placebo (NMA currently used drugs) ⊗⊗○○LOW for standardized mean difference **change in signs**, QoL ⊗○○○ VERY LOW for standardized mean difference change in itch *For azathioprine versus other drugs, see Evidence Report*		

Hintergrund:

Efficacy

The efficacy of AZA is comparable to that of MTX but lower compared to dupilumab and ciclosporin in clearing clinical signs of AE.2 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.12 However, results from retrospective studies are less favourable with a percentage of AZA treatment failure varying from 30% to 57% due to adverse effects or lack of effectiveness.13–15 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 with those without filaggrin mutations.12

Dosage: acute flare, short term, long term
We recommend combining AZA, as any systemic treatment with emollients and, whenever needed, topical antiinflammatory treatment in AE patients.
Safety
In the short and medium term, the most commonly reported serious dose-dependent effects are hepatotoxicity and myelotoxicity, together with gastrointestinal disturbances. Furthermore, idiosyncratic hypersensitivity reactions (e.g. fever, rigours, myalgia, arthralgia and occasionally pancreatitis) may occur.18 Concerns have been raised about the potential carcinogenecity induced by long-term treatment with azathioprine (predominantly squamous cell skin cancer and non-Hodgkin'slymphoma), especially if AZA is combined with other immunosuppressant regimens.19
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 and 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 fetal abnormalities has been observed. There also seems to be no effect on fertility. According to a recent position paper by ETFAD,20 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.

Ciclosporin

We **recommend** using ciclosporin to achieve disease control in AE patients who are candidates for systemic treatment.	↑↑	>75%  (19/20)[1] 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 main analysis) ⊗⊗○○ LOW for mean difference / standardized mean difference **change in signs**, Itch VAS Short term (8-16 weeks) vs placebo (NMA commonly used drugs) ⊗⊗○○LOW for standardized mean difference **change in signs**, **QoL** ⊗○○○ VERY LOW for standardized mean difference change in itch *For ciclosporin versus other drugs, see Evidence Report*		

[1]1 abstention

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%  (16/17) Expert Consensus

Hintergrund:
Efficacy
Ciclosporin has been approved for treatment of AE in adults in many European countries and is considered a first-line option for patients with severe disease if other, novel therapies are not available or indicated. Although similarly effective in the above NMA metaanalysis evaluating trials up to 16 weeks, real-life data reveal a longer drug survival of dupilumab compared with CyA after 16 months.2,26 In head-to-head trials ciclosporin was superior to MTX, prednisolone, IVIG, UVA and UVB, and similarly efficacious as EC-MPS.12,27
Dosage: acute flare, short term, long term
We recommend combining CyA, as is the case with any systemic treatment, with emollients and, whenever needed, topical anti-inflammatory treatment in AE patients.
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 and PUVA).

Systemic glucocorticosteroids

We **suggest** using systemic glucocorticosteroids *only* as rescue therapy for acute flares in AE patients.	↑	>75%  (13/17)[1] Expert Consensus
Systemic glucocorticosteroids: general unspecific licence for steroid responsive skin disease adults and children; starting dose 0.5mg/kg per day; dosage maximum: 1 mg/kg per day		
[1]1 abstention		
We **recommend against** the long-term use of systemic glucocorticosteroids in AE patients.	↓↓	100% agreement  (18/18) Expert Consensus

Hintergrund:

Efficacy

There are only few studies in adult and paediatric AE patients, despite the regular use of systemic glucocorticosteroids in clinical practice. In studies conducted in children and adults, systemic glucocorticosteroids do not induce long-term remission and swift rebound is common. Systemic glucocorticosteroids have significantly inferior efficacy than ciclosporin.24,30

Special considerations

Treatment of acute flares of AE with oral glucocorticosteroids is moderately effective.24,30 Systemic glucocorticosteroids have an unfavourable risk/benefit ratio for the long-term treatment of adult and paediatric AE.

Methotrexate

We **suggest** using methotrexate in AE patients who are candidates for systemic treatment.	↑	100% agreement  (17/17) 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 main analysis) ⊗⊗○○ LOW for standardized mean difference **change in signs** Short term (8-16 weeks) vs placebo (NMA currently used drugs) ⊗⊗○○ LOW for standardized mean difference **change in signs**, QoI ⊗○○○ VERY LOW for standardized mean difference change in itch *For methotrexate versus other drugs, see Evidence Report*		

Mycophenolate mofetil

3 months; every 2–3 months thereafter.

We **cannot make a recommendation** with respect to mycophenolate mofetil/ mycophenolic acid for the treatment of AE.	0	>75%  (16/17)[1] Expert Consensus
Mycophenolate mofetil: off licence; commonly used dosage adults: 1-3 g per day children: 30-50 mg/kg per day		
[1]1 abstention		

Biologics

Dupilumab

We **recommend** dupilumab in AE patients who are candidates for systemic treatment	↑↑	>75%  (16/17)[1] 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 main analysis) ⊗⊗⊗⊗ HIGH for mean difference/ standardized mean difference **EASI, change in signs, POEM, DLQI** ⊗⊗⊗○ MODERATE for undesirable effects Short term (8-16 weeks) vs. placebo (NMA currently used drugs) ⊗⊗⊗⊗ HIGH for standardized mean difference **change in signs, QoL, change in itch** Long term (52 weeks) vs. placebo RoB low for change in **EASI**, POEM, DLQI, undesirable effects *For dupilumab versus other drugs, see Evidence Report*		

[1] 1 abstention

Hintergrund:

Efficacy

The safety and efficacy of dupilumab was primarily established in placebo-controlled studies in moderate-to-severe AE.48 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.49 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.

Combination with other treatments

An additional phase III trial, evaluated dupilumab treatment and a concomitant topical corticosteroid (TCS) compared with placebo and a concomitant TCS over 52 weeks.54 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.48 Combination therapy with TCS, TCI, and UV light treatment is well established

Tralokinumab

We **recommend** tralokinumab in AE patients who are candidates for systemic treatment.	↑↑	100% agreement  (10/10) Evidence and consensus based, see Evidence Report
Tralokinumab: in licence for adults; Short term (8-16 weeks) vs. placebo (NMA main analysis) dosage 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]: ⊗⊗⊗○MODERATE for mean difference/ standardized mean difference **EASI**, DLQI ⊗⊗○○ LOW for undesirable effects *For tralokinumab versus other drugs, see Evidence Report*		

Hintergrund:

Efficacy

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.70 Tralokinumab monotherapy was superior to placebo at 16 weeks of treatment. Coprimary end points 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 was rerandomized 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.

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

Baricitinib

We **recommend** baricitinib in AE patients, who are candidates for systemic treatment.	↑↑	>75%  (15/16)[1] 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 main analysis) ⊗⊗⊗○MODERATE for mean difference/ standardized mean difference **EASI**, DLQI ⊗⊗⊗○MODERATE - ⊗⊗○○ LOW for undesirable effects *For baricitinib versus other drugs, see Evidence Report*		

[1]1 abstention

Hintergrund:

Efficacy

Baricitinib has been tested in one phase 2 and several phase 3 trials in adults with moderate-to severe AE at 1, 2 and 4 mg 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)]}.2 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.79

Upadacitinib

We **recommend** upadacitinib in AE patients who are candidates for systemic treatment.	↑↑	>50%  (8/15) 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 main analysis) ⊗⊗○○ LOW for mean difference **POEM** ⊗○○○VERY LOW for undesirable effects *For upadacitinib versus other drugs, see Evidence Report*		

Hintergrund:

Efficacy

In a direct head-to-head trial enrolling adult AE patients randomized to receive upadacitinib (n = 348) and dupilumab (n = 344) 24 patients receiving upadacitinib (71.0%) and 210 patients receiving dupilumab (61.1%) achieved EASI-75 at 16 weeks (P = 0.006). 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.

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.85 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 30 mg, 2.4% for 15 mg, 4.8% for 7.5

mg and 2.4% for placebo. Low withdrawal rates were reported in the placebo and upadacitinib groups (n < 5 for each group).

Abrocitinib is currently licensed for AE in those aged 12 and above in the United Kingdom. The EMA Committee for Medicinal Products for Human Use adopted a positive opinion on 14 October 2021, for adults only. As this approval came through after our consensus conferences, no consensus recommendation has been included in this iteration of the guideline.

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

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

Omalizumab

We **cannot make a recommendation** with respect to the use of omalizumab for the treatment of AE.	0	100% agreement  (17/17) 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.

Other systemic treatment

Alitretinoin

We **suggest** alitretinoin for AE patients with severe chronic hand eczema, who are candidates for systemic treatment, duely considering its teratogenicity.	↑	>75%  (14/15) Expert consensus

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

Hintergrund:
Efficacy
There is one large, multicenter randomized, placebocontrolled clinical trial involving 1032 patients with chronic hand eczema, about one-third of which were probably atopic hand eczema patients.92 Improvement of eczema was seen in 75% of the patients. The patient group suffering from atopic hand eczema was not analysed separately, and extrapalmar symptoms have not been assessed in this trial.
Six patients with AE and prominent hand involvement were treated with alitretinoin for 12 weeks in an uncontrolled, open-label trial.93 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.

Topical drugs

Table 2 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 [18])
↑↑	We believe that all or almost all informed people would make this choice.
↑	We believe that most informed people would make this choice, but a substantial number would not.
0	We cannot make a recommendation.
↓	We believe that most informed people would make a choice against this intervention, but a substantial number would not.
↓↓	We believe that all or almost all informed people would make a choice against this intervention.
	No recommendation.

Anti-inflammatory treatment

We recommend the use of topical corticosteroids (TCS) as anti-inflammatory agents. **We recommend** the use of topical calcineurin inhibitors (TCI) as anti-inflammatory agents.	↑↑	>75%  (24/26) Expert consensus
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% agreement (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% agreement (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% agreement (22/22) Expert consensus

Hintergrund Topical calcineurin inhibitors:

Efficacy

Two topical calcineurin inhibitors (TCI) (tacrolimus ointment and pimecrolimus cream) are licensed for AE treatment. TCI are a first-line therapy for sensitive areas where TCS use is likely associated with side-effects or in areas where TCS has already caused side-effects. The efficacy of both formulations has been demonstrated against vehicle in clinical trials for short-term (3 weeks)59,60 and long-term use up to 1 year.61,62

Safety

Safety data of both TCI have been reported in many clinical trials and registries, and high-quality long-term safety data have been published from 10-year tacrolimus and 5-year pimecrolimus studies, demonstrating the safety of this anti-inflammatory treatment in daily practice.73,74 None of the TCI induce skin atrophy.75,76 This favours their use over TCS in sensitive body areas such as the eyelid region, the perioral skin, the genital area, the axilla region or the inguinal fold, and makes them suitable for long-term management. In addition, the use of TCI may potentially reverse some of the side-effects of TCS when applied on sensitive areas.77 The application of TCI is not associated with an increased risk of non-melanoma skin cancer, other malignancies or photocarcinogenicity.74,80–84

Basic emollients and moisturizers

We recommend gentle cleansing and bathing procedures especially in acutely inflamed or superinfected skin in patients with AE.	↑↑	100% agreement  (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% agreement  (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] Abstention

We recommend to apply emollients immediately after bathing or showering and soft pat drying ('soak and seal technique').	↑↑	100% agreement  (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] Abstention

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 that other phototherapy modalities (balneophototherapy, UVAB, BB-UVB, UVA) are to be considered as a second choice.	↑	100% agreement  (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% agreement  (25/25) Expert consensus
We suggest co-treatment with topical emollients during phototherapy.	↑	100% agreement  (25/25) Expert consensus
We recommend against the use of prolonged or repeated treatment cycles and maintenance regimens with all phototherapy modalities.	↓↓	100% agreement  (24/24) Expert consensus
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% agreement  (25/25) Expert consensus

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 6 of 12, June 2023) am 28.06.2023

#	Suchfrage
#1	[mh dermatitis]
#2	[mh "skin diseases, eczematous"]
#3	[mh "hand dermatoses"]
#4	(eczema* OR dermatit* OR dermatos*):ti,ab,kw
#5	#1 OR #2 OR #3 OR #4
#6	#5 with Cochrane Library publication date Between Jun 2018 and Jun 2023, in Cochrane Reviews

Systematic Reviews in PubMed am 28.06.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	dermatitis[mh]
2	skin diseases, eczematous[mh]
3	eczema*[tiab] OR dermatit*[tiab] OR dermatos*[tiab]
4	hand[mh]
5	hand[tiab] OR hands[tiab] OR finger*[tiab]
6	(#1 OR #2 OR #3) AND (#4 OR #5)
7	hand dermatoses[mh]
8	#6 OR #7
9	(#8) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND

#	Suchfrage
	(literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
10	(#9) AND ("2018/06/01"[PDAT] : "3000"[PDAT])
11	(#10) NOT "The Cochrane database of systematic reviews"[Journal]
12	(#11) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 28.06.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	dermatitis[mh]
2	skin diseases, eczematous[mh]
3	hand dermatoses[mh]
4	eczema*[tiab] OR dermatit*[tiab] OR dermatos*[tiab]
5	#1 OR #2 OR #3 OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
7	(#6) AND ("2018/06/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 28.06.2023

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.0