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S3-Leitlinie

Klassifikation, Diagnostik und Therapie der Urtikaria – Leitlinienreport

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Guideline development report: German Adaptation of the International S3 Guideline for the Definition, Classification, Diagnosis and Treatment of Urticaria

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Table of contents

Introduction

This report describes the methods and processes used to develop the 2022 German adaptation (AWMF Registry No. 013/028) of the evidence- and consensus-based (S3) International EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria.[1]

When citing the German adaptation of the guideline, please use the reference below that fits the language version you are referring to:

- German version:
    - Zuberbier et al. Deutsche S3-Leitlinie zur Klassifikation, Diagnostik und Therapie der Urtikaria, adaptiert von der internationalen S3-Leitlinie, 2022. AWMF-Leitlinienregister (013-028).
- International version:
    - Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al. The international EAACI/GA²LEN/ EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2021;00:1–33. doi:10.1111/all.15090

Nomination of experts

Experts were nominated by a range of national societies in Germany and Austria (see Table 1). To be eligible for nomination and participation, the experts had to fulfil at least one of the following criteria:

- Extensive clinical experience in the diagnosis and treatment of urticaria
- Relevant publications in the field of urticaria
- Relevant experience in evidence-based medicine

Additionally, two patient representatives from the patient organisation Urtikaria-Helden e.V. joined the guideline development group and had one vote each.

Table 1: Guideline Development Group

Name	Institutional affiliation	Medical society / Organisation
Expert members of Guideline Development Group		
PD Dr. Sabine Altrichter	Kepler Universitätsklinikum Linz	Österreichische Gesellschaft für Allergologie (ÖGAI)*
Prof. Dr. Randolf Brehler	Universitätsklinikum Münster	Ärzteverband Deutscher Allergologen (AeDA)*
Prof. Dr. Knut Brockow	Klinikum rechts der Isar der Technischen Universität München	Deutsche Dermatologische Gesellschaft (DDG)*
Prof. Dr. Joachim Fluhr	Charité – Universitätsmedizin Berlin	Gesellschaft für Dermatopharmazie (GD)*
Prof. Dr. Eckard Hamelmann	Universitätsklinikum OWL der Universität Bielefeld	Deutsche Gesellschaft für Allergologie und Klinische Immunologie (DGAKI)
Prof. Dr. Marcus Maurer	Charité – Universitätsmedizin Berlin	Deutsche Gesellschaft für Allergologie und Klinische Immunologie (DGAKI)*
Prof. Dr. Hans Merk	Universitätsklinik RTWH Aachen	Ärzteverband Deutscher Allergologen (AeDA)*
Norbert K. Mülleneisen	Asthma und Allergie Zentrum Leverkusen	Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V. (DGP)*
Prof. Dr. Heidi Olze	Charité – Universitätsmedizin Berlin	Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Halschirurgie e.V. (DGHNO-KHC)*
PD Dr. Hagen Ott	Kinder- und Jugendkrankenhaus Auf der Bult Hannover	Gesellschaft für pädiatrische Allergologie und Umweltmedizin (GPA) / Deutsche Gesellschaft für Kinder- und Jugendmedizin (DGKJ)*
Prof. Dr. Oliver Pfaar *(stellvertr. Mandatsträger)*	Universitätsklinikum Marburg	Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Halschirurgie e.V. (DGHNO-KHC)
Dr. Marc Pleimes	Kinderdermatologie Praxis Heidelberg	Deutsche Gesellschaft für Kinder- und Jugendmedizin (DGKJ)*
Prof. Dr. Franziska Ruëff	LMU Klinikum der Universität München	Ärzteverband Deutscher Allergologen (AeDA)*
Prof. Dr. Petra Staubach-Renz	Universitätsmedizin Mainz	Urtikaria Netzwerk e.V. (UNEV)*
Prof. Dr. Bettina Wedi	Medizinische Hochschule Hannover	Deutsche Dermatologische Gesellschaft (DDG)*
Prof. Dr. Torsten Zuberbier	Charité – Universitätsmedizin Berlin	Deutsche Gesellschaft für Allergologie und Klinische Immunologie (DGAKI)*
Patient representatives		
Sabine Bauer	Patient representative	Urtikaria-Helden e.V.*
Kathrin Kühne	Patient representative	Urtikaria-Helden e.V. *
Methodologists		
Martin Dittmann	Division of Evidence-Based Medicine (dEBM), Charité – Universitätsmedizin Berlin	Information specialist, Guideline Office
Dr. Corinna Dressler, MSc	Division of Evidence-Based Medicine (dEBM), Charité – Universitätsmedizin Berlin	Methodologist
Matthew Gaskins, MPH	Division of Evidence-Based Medicine (dEBM), Charité – Universitätsmedizin Berlin	Methodologist
Prof. Dr. Alexander Nast	Division of Evidence-Based Medicine (dEBM), Charité – Universitätsmedizin Berlin	Methodologist, methodological coordination, facilitation of consensus conference
** entitled to vote*		

Management of conflicts of interest

All members of the guideline development group completed conflict of interest forms via the online portal before the guideline development work began. The forms were developed by the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen

Medizinischen Fachgesellschaften e.V., AWMF) specifically for use in the development of clinical practice guidelines.[2]

The conflicts of interest of all members of the Guideline Development Group were assessed by the methodological coordinator Prof. Dr. Alexander Nast. The conflicts of interest of Prof. Dr. Alexander Nast were assessed by Dr. Ricardo N. Werner. Potential conflicts of interests were classified as minimal, moderate or severe, as recommended by the AWMF according the following criteria (see Table 2).

Table 2: Criteria for assessment of conflicts of interest

<table>
<tr><th></th><th>No COI</th><th>Minimal COI</th><th>Moderate COI</th><th>Serious COI</th></tr>
<tr><td>Consulting activities</td><td>-</td><td>-</td><td rowspan="2">Personal honoraria ≤ €15,000 per year (on average)</td><td rowspan="2">Personal honoraria > €15,000 per year (on average)</td></tr>
<tr><td>Work on advisory boards</td><td>-</td><td>-</td></tr>
<tr><td>Paid lectures and/or training activities</td><td>-</td><td rowspan="2">Personal honoraria ≤ €1500 per year (on average)</td><td rowspan="2">Personal honoraria > €1500 per year (on average)</td><td>-</td></tr>
<tr><td>Paid authorships /co-authorships</td><td>-</td><td>-</td></tr>
<tr><td>Research grants/studies</td><td>-</td><td>Research grants for the clinic/institution</td><td>-</td><td>-</td></tr>
<tr><td>Owner’s interests (patents, copyrights, stock options)</td><td>-</td><td>-</td><td>-</td><td>Owner’s interests regardless of worth/amount</td></tr>
</table>

An overview of the conflict of interests of the members of the guideline development group can be found in Appendix A.

The overview of conflicts of interest was presented by the methodological coordinator of the guideline (Prof. Dr. Alexander Nast, AN) during the online consensus conference on 25 October 2021 and then discussed with the entire group. The group agreed to follow the AWMF requirements that:

(a) the group be facilitated during its meetings by a member without relevant conflicts of interest;

(b) experts abstain from voting on recommendations in which they have conflicts of interest that have been rated as moderate; and

(c) experts with severe conflicts of interest not be permitted to take part in the group.

Voting abstentions during the consensus conference were recorded in the conference protocols. These are available upon request.

Funding

The adaptation process of the guideline was funded exclusively through the guideline-funding program of the Germany Dermatological Society (Deutsche Dermatologische Gesellschaft, DDG) and the German Society for Allergology and Clinical Immunology (Deutsche Gesellschaft für Allergologie und klinische Immunologie, DGAKI). The members of the guideline development group received no payment for their work. The guideline development group worked independently and the DDG and DGAKI had no influence on the focus or content of the guideline.

National adaption process of the international guideline

A German translation of the consultation draft of the international guideline was presented to the German Guideline Development Group in a modified online Delphi voting process. We used an online survey tool (Lime Survey) to present the draft chapter by chapter. Each person was asked to read the chapter and then vote on the text and on the key questions/recommendations individually. This vote entailed either agreeing (and therefore approving) or disagreeing with the text/recommendations. In the event of disagreement, submitting alternative suggestions was mandatory. The voting results were calculated and comments collated and subsequently fed back to the group in an online consensus conference.

This online consensus conference took place on 25 October 2021. During the conference, all recommendations from international guideline were discussed and the group decided whether the text/recommendations could be accepted within the German health care setting or if there was a need for change. Cost and economic considerations were also discussed (Wirtschaftlichkeitsgebot). All relevant comments were noted, discussed one by one, and this was followed by pre-voting, final discussion and final consensus voting. The discussion was facilitated by the methodological coordinator of the guideline, Prof. Dr. Alexander Nast (AWMF Guideline Councillor), using the nominal group technique. All nominated experts in the Guideline Development Group and the patient representatives were entitled to vote. Abstentions due to conflicts of interest were noted. A strong consensus was the primary goal, which was defined a prior as >95% agreement. If that could not be achieved after extended discussion, consensus (≥75% agreement) was accepted.

The formal wording of recommendations was translated into German, as explained in Table 3.

Essentially, all recommendations were adopted from the international guideline; however, there are some minor deviations in wording due to the translation of the content from English into German, because the recommendation in question was adapted to the health care context of Germany (such as the addition of a reference to off-label use), or in one case transformed into background text.

Table 3: Wording of recommendations, symbols and implications (adapted from Kaminski-Hartenthaler et. al, 2014)[3]

Strength	Wording	Symbols	Implications
Strong recommendation **for** the use of an intervention	'We recommend . . .' **„wird empfohlen"**	↑↑	We believe that all or almost all informed people would make a choice in favour of using this intervention. Clinicians will not have to spend as much time on the process of decision-making with the patient and may devote that time instead to overcoming barriers to implementation and adherence. In most clinical situations, the recommendation can be adopted as a policy.
Weak recommendation **for** the use of an intervention	'We suggest . . .' **„kann empfohlen werden"**	↑	We believe that most informed people would make a choice in favour of using this intervention, but a substantial number would not. Clinicians and other health care providers will need to devote more time to the process of shared decision-making. Policy makers will have to involve many stakeholders and policy making will require substantial debate.
Open recommendation / No recommendation with respect to an intervention	'We cannot make a recommendation with respect to . . .' **„es kann keine Empfehlung für oder gegen … ausgesprochen werden"**	**0**	Currently, a recommendation in favour of or against using this intervention cannot be made due to certain circumstances (for example, unclear or balanced benefit-risk ratio, no data available).
Weak recommendation **against** the use of an intervention	'We suggest against . . .' **„kann nicht empfohlen werden"**	↓	We believe that most informed people would make a choice against using this intervention, but a substantial number would not.

Strong recommendation **against** the use of an intervention	'We recommend against . . .' **„wird nicht empfohlen"**	↓↓	We believe that all or almost all informed people would make a choice against using this intervention. This recommendation can be adopted as a policy in most clinical situations.

External consultation and approval of German guideline

The international S3 guideline and the German-language adaptation each underwent an extensive external review. In the former case, the review ran from 21 June 2021 to 31 July 2021 and included various national professional societies and the members of the European Dermatology Forum. In the latter case, the review ran from 1 December 2021 to 17 January 2022 and included, among others, the participating societies. In both review processes, the members of the respective guideline committees were also able to submit further comments.

All comments received were collected and reviewed by the guideline coordinators and the Guideline Methods Group. Minor editorial changes were incorporated by the Guideline Methods Group. Substantial comments were compiled in an overview document, which is available upon request. The release of the adapted version for Germany took place after review by the 2+2 Commission of the German Dermatological Society / the Professional Association of German Dermatologists as well as other participating experts and reviewers.

Dissemination, implementation and evaluation of the German guideline

The success of a guideline depends on whether it is accepted and used in clinical practice. To this end, the dissemination of the guideline will take place within the framework of the existing DDG dissemination programme. It will be available on the AWMF homepage, as well as in print and online in a peer-reviewed journal. It will also continue to be publicized and discussed in seminars and other events of the DDG, BVDD and DGAKO. Furthermore, all of the experts involved in the development of the guideline were encouraged to give talks and present the results and recommendations of the guideline at conferences.

Updating the guideline

Clinical practice guidelines should ideally be updated at regular intervals to account for changes in technologies and evidence, as well as policy and infrastructure. This version of this guideline is valid until 31 January 2025. Contact person for an update is Prof. Dr. Torsten Zuberbier (torsten.zuberbier@charite.de).

The following sections are taken from the methods report of The International EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria von Zuberbier et al. (2021),[1] available on the EuroGuiDerm website at https://www.edf.one/de/home/Guidelines/Guidelines.html (accessed 22 February 2022). They apply equally to the German setting. For the appendices mentioned below please see the methods report of the international guideline, as well.

Search methods, search results and evidence selection

Search

The key questions were translated into the PICO format, which specifies the intervention, comparison and outcome used to assess efficacy and safety (see box 1). The PICO is specified in the header of each evidence-to-decision framework. Systematic searches for randomized controlled trials and clinical, controlled trials were undertaken using the following databases on 15 May 2020 limiting the time to 2016 – 15 May 2020:

- Ovid MEDLINE(R) ALL 1946 to May 14, 2020
- Embase Classic+Embase 1947 to 2020 May 14
- Cochrane Central Register of Controlled Trials (CENTRAL)

All search strategies can be found in Appendix 1: Search Strategies (Note: See the methods report of the international guideline; an example search strategy for Embase can also be found at the end of the present document). We did not search trials registries, grey literature sources, or contact authors due to resource limitations. EndNote X9™ was used to manage references.

Because the Update of the EAACI/GA²LEN/EuroGuiDerm/APAAACI International Guideline for Urticaria is an update of an existing guideline, we did not search for other guidelines or systematic reviews.

Eligibility criteria

The pre-selected inclusion criteria for the title/abstract and full-text screening are given in Box 1. The exclusion criteria for the title/abstract and full-text screening are given in Box 2.

Box 1: PICO / inclusion criteria

Population

Patients of all ages and genders with:

- chronic spontaneous urticaria (CSU) (a.k.a. chronic idiopathic/chronic urticaria)
- chronic inducible urticaria (CindU) (i.e. cold urticaria, pressure urticaria, heat urticaria, solar urticaria, symptomatic dermographism (=urticaria factitia), vibratory angioedema, aquagenic urticaria, cholinergic urticaria, contact urticaria)
- angioedema without wheal

Interventions (stated with minimum standard dosage for adults, where applicable)

H1-antihistamines (H1-AH) 1st generation:

- clemastine fumarate 1mg BID (≙ 1.34mg clemastin fumarate), 20ml sirup BID (≙ 1.34mg clemastine hydrogen fumarate = 1mg clemastine); dimetindene maleate 0.05-0.1mg/kg BW QD (≙ 1-2 dragees à 1mg dimetindene maleate), 1ml TID (≙ 20 drops); diphenhydramine; hydroxycine dihydrochloride 37.5mg (≙ 1,5 tablets; 25mg ≙ 20.93mg hydroxycine); ketotifen fumarate (HC 20-511 Sandoz) 1.38mg (≙ 1 capsule)

H1-antihistamines 2nd generation:

- acrivastin 8mg TID; bilastine 20mg QD (≙ 1 tablet); cetirizine dihydrochloride 10mg QD (≙ 1 tablet ≙ 8.42mg cetirizine)/ 10mg sirup QD (1ml sirup ≙ 1mg cetirizin-$_2$HCl); desloratadine 5mg QD (≙ 1 tablet); ebastine 10mg QD (≙ 1 tablet); emedastine 2mg BID (≙ 1 drop BID; 1ml solution ≙ 0.5mg emedastine [0.05%] as difumarate [0.884mg/1ml emedastine difumarate]); fexofenadine 180mg QD (≙ 1 tablet); levocetirizine dihydrochloride 5mg QD (≙ 1 tablet ≙ 4.2mg levocetirizine); loratadine 10mg QD (≙ 1 tablet); mizolastine 10mg QD (≙ 1 tablet); rupatadine 10mg QD (≙ 1 tablet ≙ 12.79mg rupatadine fumarate)

Other therapies:

- anakinra (100mg) in 0.67ml (150 mg/ml) syringe; autologous whole blood (AWB)/ autologous serum/ autohemotherapy; colchicine; cyclosporine; dapsone; doxepine 50mg QD (≙ 5 tablets; 1 tablet ≙ 11.31mg rupatadine fumarate); heparin; hydroxychloroquine; intravenous immunoglobulins (IVIG); methotrexate; montelukast 10mg (≙ 10.38mg montelukast sodium); omalizumab 150mg and 300mg per month (100mg omalizumab ≙ 1ml solution in syringe); oral corticosteroids (prednisone, prednisolone, methylprednisolone, triamcinolone, betamethasone, dexamethasone); phototherapy: UVB, narrow band-UVB, PUVA; rituximab (50ml contain 500mg rituximab [CHO-cells]); sulfasalazine; tacrolimus; TNF-alpha inhibitors: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab

Comparisons

- 2nd generation H1-AH vs. placebo
- 2nd generation H1-AH vs. 1st generation H1-AH
- Low dose 2nd generation H1-AH vs. high-dose 2nd generation H1-AH (up to 4-fold)
- H1- AH vs. other therapies
- H1-AH vs. H1-AH combined with other therapies (other therapies refers to those listed above)
- Other therapies vs. each other (other therapies refers to those listed above)

Outcomes

- Proportion of participants with complete suppression of urticaria
- Proportion of participants with 'good' or 'excellent' response
- Proportion of participants with 50% or greater improvement in quality of life measurements
- Mean reduction in Weekly Urticaria Activity Score (UAS7)
- Serious adverse events (i.e. serious enough to require withdrawal of treatment)
- Proportion of participants who relapse within one month of stopping intervention
- Minor participant-reported adverse events not requiring withdrawal of treatment, e.g. sedation

Study types

- Randomised controlled trials
- Controlled clinical trials (defined as a clinical studies that includes a comparison group)

Box 2: Exclusion criteria

- healthy volunteers with induced wheals
- urticaria pigmentosa
- food-induced allergic reaction, for example, shrimp allergy
- hereditary angioneurotic edema/ hereditary angioedema (HAE)
- contact urticaria
- diets other than as defined as pseudoallergene diet
- studies reporting outcomes at a follow-up time of more than 12 weeks only
- outcome assessment after a treatment duration shorter than 1 week
- comparisons of same medication in different treatment regime (for example verum A updosing every week versus verum B updosing every week,) or different applications (for example, tablet versus capsule)
- if only an abstract was available and no numerical data for efficacy outcomes (only p-values or text) were reported, the abstract was excluded
- if in the full-text publication (including any supplementary materials) numerical outcome data were not provided in a format suitable for ReviewManager, the full-text was excluded (for details, see methods report of the international guideline).

Screening and data extraction

Two researchers (AN, MG) independently screened the titles and abstracts of all hits for eligibility. In cases where no abstract was available and the title did not give an obvious reason for exclusion, we obtained the full-text publication. The two researchers subsequently screened the full-text publications of the included titles and abstracts for eligibility. In some cases, only abstracts were available; we included these if they met our eligibility criteria. (Note: A list of excluded studies can be provided by the research team upon reasonable request.)

Data were then extracted from the included publications by the two researchers independently of each other using a standardized data extraction form in MS Excel. These were subsequently compared and differences of opinion were resolved by discussion. The items listed in Table 4 were extracted if available in the pre-defined format. Data were transformed whenever appropriate (see below). We used Engauge Digitizer Version 4.7 to extract data points from images of graphs.

Table 4: Items for data extraction

Study characteristics and baseline data	
First author and year	First author and year of print publication
Intervention	Latin abbreviation for treatment regimen; duration of treatment as stated in publication; PBO for matched placebo and 'nothing' for no medication
Randomized or assigned patients	n (number of patients per arm)
Study design	Type of RCT or CCT, multi-centre (MC) or single-centre (SC)
Inclusion criteria disease	CIU, CSU, CU or CIndU type; extraction of full inclusion criteria from study
Inclusion criteria age	Years (as stated)
Special patient population	No; children (age), pregnant or lactating women
Washout	Duration and medication
Concomitant treatment	As stated in publication
Age at baseline	Mean±SD, median (IQR), or range (as reported in publication)
Gender distribution at baseline (female)	% (rounded off to whole numbers)
Outcomes: efficacy and HRQL data are extracted for week 1-2 and week 3 – 12	
Follow-up point in time	As stated in publication

Definition of outcome (scoring)	As stated in publication - *must be investigator assessed*
Matched outcome	State score that was matched with 'complete suppression'
Patients with complete suppression	n/N
Matched outcome	State score that was matched with 'good' or 'excellent'
Patients with at least 'good' or 'excellent' response	n/N (includes n of complete suppression)
Follow-up point in time	As stated in publication
Definition of efficacy score	As stated in publication
Mean change (SD)	Mean±SD and n / *make note of who assessed*
Follow-up point in time	As stated in publication
UAS or UAS7	state which one: UAS or UAS7 */make note of who assessed it*
Patients with ≤ 6 points	n/N
Follow-up point in time	As stated in publication
Definition of HRQL outcome	As stated in publication
Mean change (SD)	Mean±SD and n
Patients with ≥50% improvement in QoL	n/N
Outcomes: Adverse events and Relapse	
Withdrawal/drop out due to adverse event	n/N
Point in time of adverse event	As stated in publication
Patients with at least 1 adverse event	n/N
Adverse Events	Number of patients with somnolence, fatigue, drowsiness, tiredness, dizziness *for studies comparing 1st vs. 2nd gen AH only (preferable 'patient-assessed')*
Definition of relapse	Definition of relapse at time x (up to max. 6 months)
Proportion of patients relapsing at time x	n/N

Notes: CCT: controlled clinical trial; CindU: chronic inducible urticaria; CIU: chronic idiopathic urticaria; CSU: chronic spontaneous urticaria; CU: chronic urticaria; IQR: interquartile range; QoL: quality of life; RCT: randomised controlled trial; SD: standard deviation; UAS: urticaria activity score; UAS7: seven-day urticaria activity score

Statistical analysis

This section is, in large part, identical to that in the previous Methods and Evidence Report[4]

We calculated risk ratios and mean differences with the corresponding 95% confidence intervals using Review Manager 5.4.[5] Each comparison and outcome were entered into Review Manager separately, and subgroups for each point in time of evaluation were created. We included several multi-arm studies where the comparator arm was split in case of multiple comparisons to avoid counting participants more than once (only when data were later pooled). The methods offered by Review Manager are not ideal for analysing rare events (e.g., number of/proportion of patients, who experiences an adverse event). A zero-cell correction is applied or an estimation is not possible when events are zero in both groups; other statistical methods offer options, but are advanced and present own drawbacks.[6-8] Hence, we decided to calculate the risk difference instead of the risk ratio in some cases.

Decisions on appropriateness of pooling the data were made taking the PICO and the key question into consideration. We choose the Mantel-Haentzel approach using a random-effects model because the difference between the studies suggested that no common effect was assessed (DerSimionian-Laird).[9] The decision was made to pool data if heterogeneity was I^2 <= 80%. In cases were I^2 >= 40%, we downgraded during the assessment of the quality of evidence (GRADE – inconsistency criteria).

We pooled data across time points: week 1 and 2, week 3 and 4 and across week 5 and 6. Data were not pooled across 8 and 12 weeks or when the dosage changed between two time points. If multiple time points had been reported, we preferred the earliest time point in each time bracket.

Due to the different assessment scales used, we calculated an SMD where this was more appropriate.

Data transformation

We performed a variety of data transformations because the data reported in the included publications were not always in a format suitable for meta-analysis.

$$SD_{E,\,change} = \sqrt{SD^2_{E,\,baseline} + SD^2_{E,final} - (2 \times Corr \times SD_{E,\,basline} \times SD_{E,\,final})}$$

$$Corr_E = \frac{SD^2_{E,baseline} + SD^2_{E,final} - SD^2_{E,change}}{2 \times SD_{E,baseline} \times SD_{E,final}}$$

In order to calculate summary measures for continuous outcomes, a measure of dispersion, i.e. the standard error or the standard deviation (SD) had to be available. For continuous outcomes the absolute mean change in a score from baseline could be calculated where baseline and final data were provided. The corresponding standard deviation could only be calculated using the formula below if we were able to use data from another publication and calculate a correlation coefficient assuming that the intervention did not change the variability of the outcome measures, as suggested by Cochrane.[10]

Otherwise missing standard deviations for mean changes were calculated based on the confidence interval and the standard error. If only the baseline mean value ± SD and the end mean value without SD (i.e., was digitised from a chart) was available or the final mean ± SD but no SD for the mean change was reported or calculable, no effect measure could be calculated. Concerning dichotomous efficacy outcomes, we calculated a non-responder-imputation-based ITT to harmonize the data pool.

$$SE = (\text{upper limit CI} - \text{lower limit CI}) / 3.92$$

$$SD = SE \times \sqrt{N}$$

Mean change was always preferred, but if not available or the above calculations were not possible, we pooled the final mean and mean change.

Critical appraisal of evidence

Risk of bias assessment

The data extraction sheet also contained the categories of the Cochrane Risk of Bias Assessment Tool,[11] which we used to assess *sequence generation*, *allocation concealment* and *other sources of bias* at the

study level, and *blinding of patients and personnel* and *blinding of outcome assessment* at the outcome level. For the specific decision-making criteria used to make the assessments, please refer to the previous Methods and Evidence Report.[4] We used the ROBINS – I tool for non-randomized clinical controlled trials.[12]

GRADE Assessment of the quality of evidence

The GRADE approach was used to appraise the quality of evidence and develop evidence-to-decision frameworks.[13] We used the online application GRADE pro GDT[14] to create GRADE evidence profiles for each comparison. During this process, the following five criteria were used to rate each outcome as *not serious*, *serious* (downgraded by 1 level) or *very serious* (downgraded by 2 levels). Randomized, controlled trials (RCT) start with the highest rating (not serious). A summary of the criteria influencing the quality and the different quality levels are displayed in Table 5 (adapted from Bashem et al. 2001[15]). Each criterion that may decrease the quality rating is described in detail below.

Table 5: Summary of the GRADE approach to assessing the quality of evidence by outcome in randomised controlled trials[15]

Initial quality of the body of evidence	Criteria that may decrease the quality rating	Criteria that may increase the quality rating	Quality of the body of evidence	
High	– Risk of bias – Inconsistency – Indirectness – Imprecision – Publication bias	– Large effect – Dose response – Residual confounding	High (++++)	We are very confident that the true effect lies close to that of the estimate of effect.
			Moderate (+++)	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.

1. Risk of bias: The Cochrane Risk of Bias Assessment tool was used. We downgraded if several risk of bias items were deemed unclear and/or high. Where more than one study had been included in a meta-analysis, we looked at the weights assigned in the meta-analysis to help determine the overall risk of bias.

2. Inconsistency: If only one study was available, we could not assess inconsistency. No default option for this case is available; hence, we rated inconsistency as *not serious.* If more than one study was included, we downgraded to *serious* if statistical heterogeneity was detected as $I^2 \geq 40\%$ and to *very serious* if $I^2 \geq 70\%$.

3. *Indirectness*: Only if the population and/or intervention specified in the key question differed from the population and/or intervention in the studies included did we downgrade to *serious*. For example, if a study included non-responders to different doses of H1-AH but the PICO question had specified for the population to be non-responder to high doses of H1-AH did we downgrade.

4. Imprecision: Imprecision was rated as *serious* if the confidence interval was very wide (for example, 0.06 to 15.14 or 2.05 to 97.04). In addition, the boundaries of the calculated confidence intervals were assessed. The GRADE approach postulates for the minimal clinical important difference (MID) thresholds to be larger than 25% benefit (1.25) and 25% harm (0.75).[15] If the confidence interval crossed the MID threshold this represents uncertainty in regards to clinical importance. If one or both MID thresholds were crossed, we downgraded to *serious*. If only the line of no effect was crossed but no MID threshold, we did not downgrade because the result is precise.

For continuous outcomes, we based our assessment on MID thresholds that are anchor-based and available in the peer-reviewed literature. For the Dermatology Quality of Life Index with a possible range of scores from 0 to 30, the MID threshold used was 3 (Shikiar et al. 2005 suggested 2.2 to 3.2; [16]). For the Urticaria Activity Score 7 (UAS7) Mathias et al. 2012 had suggested an MID range from 9.5 to 10.5, we used 10.[17] In cases where we calculated the risk difference for rare events (for example for AEs), we used a 2% as the MID. When we used the SMD, we used - 0.2 / 0.2 (as small effect, see Cohen).

Where no anchor-based MIDs were available, we used distribution-based MIDs, namely ½ the SD.[18] We did not downgrade the quality rating for imprecision in the case of zero events.

5. Publication bias: Due to the small number of studies whose data were pooled for most comparisons, we were unable to assess publication bias, for example, using a funnel plot and rated this form of bias as 'undetected'.

Just as we used each PICO question to create a GRADE evidence profile (or set of such profiles), so too did we use each GRADE evidence profile to develop an Evidence-to-Decision (EtD) framework. These aimed to help the members of the expert panel (a) make an overall judgement regarding the size of the desirable and undesirable effects of specific comparisons and the balance between the two, (b) summarize the overall quality of the evidence, and (c), in doing so, develop the evidence- and consensus-based guideline recommendations and accompanying background texts.

Results of the evidence update

The literature search on 15 May 2020 identified 2053 records. The removal of duplicates left 1602 records for the title/abstract screening, of which 1458 were excluded. This left 144 records to be assessed as full texts for eligibility, of which 123 were excluded. A list of excluded full-text publications with reasons for exclusion can be found in Figure 1. A total of 21 records were ultimately included in the evidence-based review. These comprised (a) 13 new studies reporting data on treatments for CSU and two studies reporting additional data to that included in the 2017 guideline and (b) two new studies reporting data on treatments for CINDU and one study reporting additional data to that included in the 2017 guideline. Of the former group, one study was excluded at the data extraction stage because it did not report the requisite dispersion measures.[19] A breakdown of this process can be seen in the study selection flowchart in Figure 1. Additionally, in the EtD frameworks, an asterisk (*) after an author-year reference or a particular outcome indicates where new data were identified or added to existing data as part of the 2020/21 update of the guideline.

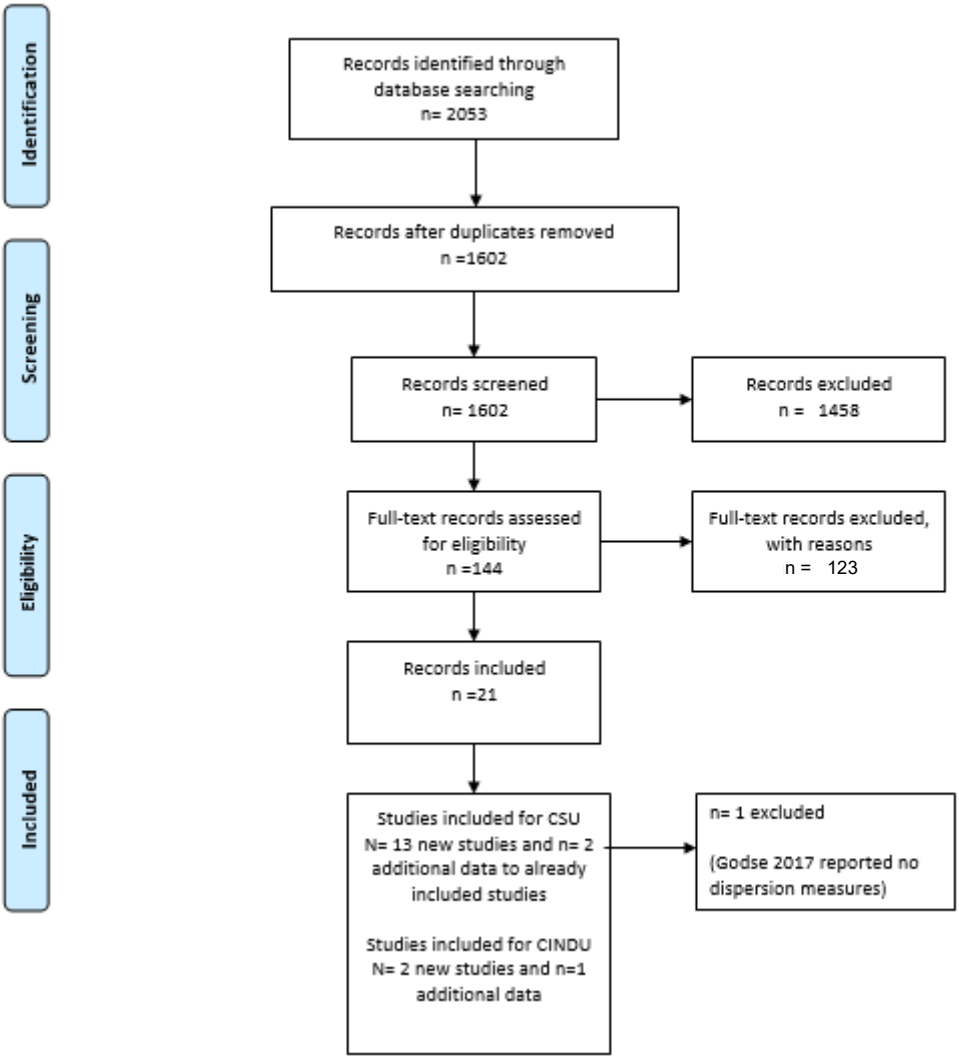

Figure 1. Study selection flowchart

We created a total of 14 new or updated GRADE evidence profiles and 14 new or updated EtD frameworks. A summary of the evidence is given in the Evidence Report, which is available on the EDF website (https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html).

[…]

Strengths and limitations

This section is, in large part, identical to that in the previous Methods and Evidence Report[4]

The strength of the body of evidence presented lies within the application of rigorous and systematic methods as recommended by Cochrane and the GRADE working group, which we describe in detail here. We also used Evidence to Decisions Frameworks to include the balance of potentially desirable and undesirable effects as well as to raise awareness about the feasibility, costs, equity and acceptability of the intervention. These barriers to implementation need to be considered within the national or local context.

The evidence identified regarding the treatment of urticaria is very diverse and many studies report different outcomes at different time points. The reader should be aware of the issue of multiplicity, although we specified outcomes and time points a priori in the protocol. There were no protocol amendments or deviations from the protocol.

Concerning statistical limitations, for different comparisons we did pool two trials although the detection of heterogeneity using the I^2 statistics is suboptimal. It is also worth mentioning that the UAS7 is scored in two different ways. When pooling data, we did not differentiate between these two systems. However, Karsten Weller (expert, Weller et al [unpublished data]) found that these two scoring systems are very similar. With regard to the assessment of various outcomes, some trials did not report whether the outcome was patient or physician-assessed. Each unclear case was debated within the review team and a pragmatic approach was chosen when handling the data.

Due to resource restrictions we neither searched for further evidence by hand nor did we search grey literature repositories or trial registers. However, a large number of experts were involved in the guideline development process, and no missing or ongoing trials were evident. The review protocol specified that each primary study had to report the necessary data to be able to calculate effect measures. Reporting was often suboptimal and studies had to be excluded. We did not qualitatively report on these studies, and this choice may have introduced reporting bias.

During the guideline development process, no patient representative or patient organization was involved, although we did attempt to invite patient representative from the European Federation of

Allergy and Airways Diseases Patients‘ Associations (EFA). (Addendum regarding the German adaptation of the guideline: For the adaptation, two patient representative from the Urtikaria-Helden e.V. took part in the development of the guideline and were voting members of the guideline development group.)

Example search strategy

Database: Embase Classic+Embase 1947 to 2020 May 14

1. exp *Urticaria/

2. "urticaria*".ab,kw,ti.

3. hives.ab,kw,ti.

4. w?eals.ab,kw,ti.

5. "dermatographi*".ab,kw,ti.

6. ("factiti*" adj3 urticaria*).ab,kw,ti.

7. ((cold or heat or pressure or solar) adj3 urticaria*).ab,kw,ti.

8. (vibratory adj3 angio?edema).ab,kw,ti.

9. ((cholinergic or contact) adj3 urticaria*).ab,kw,ti.

10. ((aquagenic or (water adj3 induc*)) adj3 urticaria*).ab,kw,ti.

11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12. Randomized controlled trial/

13. Controlled clinical study/

14. random$.ti,ab.

15. randomization/

16. intermethod comparison/

17. placebo.ti,ab.

18. (compare or compared or comparison).ti.

19. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.

20. (open adj label).ti,ab.

21. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

22. double blind procedure/

23. parallel group$1.ti,ab.

24. (crossover or cross over).ti,ab.

25. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.

26. (assigned or allocated).ti,ab.

27. (controlled adj7 (study or design or trial)).ti,ab.

28. (volunteer or volunteers).ti,ab.

29. human experiment/

30. trial.ti.

31. or/12-30

32. random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)

33. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)

34. (((case adj control$) and random$) not randomi?ed controlled).ti,ab.

35. (Systematic review not (trial or study)).ti.

36. (nonrandom$ not random$).ti,ab.

37. “Random field$”.ti,ab.

38. (random cluster adj3 sampl$).ti,ab.

39. (review.ab. and review.pt.) not trial.ti.

40. "we searched".ab. and (review.ti. or review.pt.)

41. "update review".ab.

42. (databases adj4 searched).ab.

43. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/

44. Animal experiment/ not (human experiment/ or human/)

45. or/32-44

46. 31 not 45

47. 11 and 46

48. ("201604*" or "201605*" or "201606*" or "201607*" or "201608*" or "201609*" or "201610*" or "201611*" or "201612*" or "2017*" or "2018*" or "2019*" or "2020*").dc.

49. 47 and 48

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Appendix A: Declarations of Interest

	Berater-bzw. Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer-interessen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Einstufung bzgl. der Relevanz zu den Leitlinienkapiteln
PD Dr. Sabine Altrichter	Ja	Nein	Ja	Nein	Nein	Nein	Mitglied: Urtikaria-Netzwerk UNEV, Urtikaria-Verband / Selbsthilfegruppe	Diagnostik: Keine Therapie: Gering
Sabine Bauer	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: -	Diagnostik: Keine Therapie: Keine
Prof. Dr. Randolf Brehler	Ja	Ja	Ja	Nein	Ja	Nein	Mitglied: ÄDA, DGAKI, EAACI, DKG	Diagnostik: Keine Therapie: Moderat
Prof. Dr. Knut Brockow	Nein	Ja	Ja	Nein	Nein	Nein	Mitglied: EAACI, DGAKI, DAAB, AGATE, Deutsches Kompetenznetzwerk Mastozytose	Diagnostik: Moderat Therapie: Gering
Martin Dittmann	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: -	Diagnostik: Keine Therapie: Keine
Dr. Corinna Dressler, MSc	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: -	Diagnostik: Keine Therapie: Keine
Prof. Dr. Joachim Fluhr	Ja	Nein	Nein	Nein	Nein	Nein	Mitglied: GD	Diagnostik: Moderat Therapie: Keine
Matthew Gaskins, MPH	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: -	Diagnostik: Keine Therapie: Keine
Prof. Dr. Eckard Hamelmann	Nein	Ja	Ja	Nein	Nein	Nein	Mitglied: DGAKI, GAN, GPP, GPA	Diagnostik: Moderat Therapie: Moderat
Kathrin Kühne	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: -	Diagnostik: Keine Therapie: Keine

	Berater-bzw. Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer-interessen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Einstufung bzgl. der Relevanz zu den Leitlinienkapiteln
Prof. Dr. Marcus Maurer	Ja	Ja	Ja	Nein	Nein	Nein	Mitglied: EEACI, EADV, GA2LEN, ADF, ANEV, CIA, EMBRN, PID, UNEV, DHA	Diagnostik: Moderat Therapie: Moderat
Prof. Dr. Hans Merk	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: Leopoldina, DDG, EADV, EAACI, ADF, AAD, SID, ESDR, SOT, AAAAI, AeDA, DGAKI	Diagnostik: Keine Therapie: Keine
Norbert K. Mülleneisen	Nein	Nein	Ja	Nein	Nein	Nein	Mitglied: AeDA, UEMS, Regionales Praxisnetz Leverkusen, KV Leverkusen	Diagnostik: Keine Therapie: Gering
Prof. Dr. Alexander Nast	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: DDG, EADV, EDF, dNEbM	Diagnostik: Keine Therapie: Keine
Prof. Dr. Heidi Olze	Nein	Ja	Ja	Nein	Nein	Nein	Mitglied: DGHNO, GA2LEN	Diagnostik: Keine Therapie: Moderat
PD Dr. Hagen Ott	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: GPA, NAPPA, DGAKI	Diagnostik: Keine Therapie: Keine
Prof. Dr. Oliver Pfaar	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: EEACI, DGHNO-KHC, EUMETNET	Diagnostik: Keine Therapie: Keine
Dr. Marc Pleimes	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: Netzwerk interdisziplinäre pädiatrische Dermatologie, DGKJ	Diagnostik: Keine Therapie: Keine
Prof. Dr. Franziska Ruëff	Nein	Ja	Ja	Nein	Nein	Nein	Mitglied: EAACI, DGAKI, ABD, AEDA, DDG	Diagnostik: Moderat Therapie: Moderat
Prof. Dr. Petra Staubach-Renz	Ja	Ja	Ja	Nein	Nein	Nein	Mitglied: DDG, EADV, GD, NRF , BVDD	Diagnostik: Keine Therapie: Moderat
Prof. Dr. Bettina Wedi	Nein	Ja	Ja	Nein	Nein	Nein	Mitglied: DGAKI, DDG, ADF, EAACI, Deutsche Gesellschaft für Angioödeme	Diagnostik: Gering Therapie: Moderat

	Berater-bzw. Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer-interessen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Einstufung bzgl. der Relevanz zu den Leitlinienkapiteln
Prof. Dr. Torsten Zuberbier	Ja	Ja	Ja	Nein	Nein	Nein	Mitglied: GA2LEN, DGAKI, DAAU, ECARF, EAACIa	Diagnostik: Moderat Therapie: Moderat

Versions-Nummer: **3.0**

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