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GUIDELINE

S3 Guideline Urticaria. Part 2: Treatment of urticaria – German-language adaptation of the international S3 guideline

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Professional Societies involved:

AeDA – Ärzteverband Deutscher Allergologen (Medical Association of German Allergologists)

DDG – Deutsche Dermatologische Gesellschaft (German Dermatological Society)

DGAKI – Deutsche Gesellschaft für Allergologie und Klinische Immunologie (German Society for Allergology and Clinical Immunology)

DGHNO-KHC – Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Halschirurgie (German Society for Ear, Nose and Throat Medicine, Head and Neck Surgery)

DGKJ – Deutsche Gesellschaft für Kinder- und Jugendmedizin (German Society for Pediatric and Adolescent Medicine)

Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (German Society for Pneumology and Ventilation Medicine)

GD – Gesellschaft für Dermatopharmazie (Society for Dermatopharmaceutics)

GPA – Gesellschaft für pädiatrische Allergologie und Umweltmedizin (Society for Pediatric Allergology and Environmental Medicine)

ÖGAI – Österreichische Gesellschaft für Allergologie (Austrian Society for Allergology)

UNEV – Urtikaria Netzwerk e.V. (Urticaria Network)

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Summary
This publication is the second part of the German-language S3 guideline on urticaria. It covers the management of urticaria and should be used together with Part 1 of the guideline on classification and diagnosis. This publication was prepared according to the criteria of the AWMF on the basis of the international English-language S3 guideline with special consideration of health system conditions in German-speaking countries. Chronic urticaria has a high impact on the quality of life and daily activities of patients. Therefore, if causal factors cannot be eliminated, effective symptomatic treatment is necessary. The recommended first-line treatment is to administer new generation, non-sedating H1 antihistamines. If the standard dose is not sufficiently effective, the dose should be increased up to fourfold. For patients who do not respond to this treatment, the second-line treatment in addition to antihistamines in the treatment algorithm is omalizumab and, if this treatment fails, ciclosporin. Other low-evidence therapeutic agents should only be used if all treatments in the treatment algorithm agreed upon by the guideline group fail. Both the benefit-risk profile and cost should be considered. Corticosteroids are not recommended for long-term treatment due to their inevitable severe side effects.

INTRODUCTION

This publication is the second part of the German-language S3 guideline on urticaria. It covers the management of urticaria and should be used together with Part 1 of the guideline on classification and diagnosis. This German guideline has been prepared according to the criteria defined by the Working Group of Scientific Medical Societies (AWMF, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften). It is based on the international S3 guideline (*The international EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria*), which was published in October 2021. It has been adapted to the situation in the German-speaking countries and consists of two separate sections: Part 1 covering the classification and diagnostics of urticaria, and part 2 (this publication) focusing on the treatment of urticaria. Altogether, the guideline offers an overview of expert-led and evidence-based diagnostic and therapeutic approaches for the different subtypes of urticaria.

During the international consensus meeting on 3rd December 2020 in Berlin, the German-language authors were represented either in the on-site committee or in the online auditorium. After the English-language version had become available, this was translated and the translation agreed upon before being used as a basis for preparing the German guideline. The German-language guideline follows the international version as far as possible and was prepared, commented and adapted for the German-speaking countries as an S3 guideline according to the AWMF criteria.

Part 2 of this guideline concentrates on the management of urticaria. Chronic urticaria has a high impact on the quality of life and daily activities of patients. Therefore, if causal factors cannot be eliminated, effective symptomatic treatment is necessary. The recommended first-line treatment is to administer new generation non-sedating H1 antihistamines. If the standard dose is not sufficiently effective, the dose should be increased up to fourfold. For patients who do not respond to this treatment, the second-line treatment in addition to antihistamines in the treatment algorithm is omalizumab and, if this treatment fails, ciclosporin. Other low-evidence therapeutic agents should only be used if all treatments in the treatment algorithm agreed by the guideline group fail. Both the benefit-risk profile and cost should be considered. Corticosteroids are not recommended for long-term treatment due to their inevitable severe side effects.

TABLE 1 Recommendation strengths – wording, symbols, and interpretation.

Strength of Recommendation	Wording	Symbol	Interpretation
Strong recommendation for the use of an intervention	"We recommend …"	↑↑	We believe that all or almost all informed people would make a choice in favor 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 …"	↑	We believe that most informed people would make a choice in favor of using this intervention, but a substantial number would not. Clinicians and other healthcare 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.
No recommendation with respect to an intervention	"We cannot make a recommendation with respect to…"	0	Currently, a recommendation in favor of or against using this intervention cannot be made due to certain circumstances (e.g. unclear or balanced benefit-risk ratio, no data available).
Weak recommendation against the use of an intervention	"We suggest against …"	↓	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…"	↓↓	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.

Modified according to Kaminski-Hartenthaler et al. (2014).[3]

METHODS

Please refer to the guideline report for further information (online supplement at www.awmf.org). This guideline is adapted from the S3 guideline "*The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria*" by Zuberbier et al. (2021).[1] The final version of this international guideline has been published at https://doi.org/10.1111/all.15090 and is available on the website of the European Dermatology Forum (https://www.edf.one/home/Guidelines/Guidelines.html) (licensed under CC BY NC 4.0, https://creativecommons.org/licenses/by-nc/4.0/).

Some sections of this guideline were taken from the international S3 guideline without any changes. The international guideline has been prepared according to the EuroGuiDerm Methods Manual v1.3. The manual is available on the European Dermatology Forums (EDF) homepage (https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html).

Standardized terms, adapted from the "Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group", have been used to achieve consistent wording for all recommendations;[2] please also refer to the overview in Table 1.

Every recommendation with consensus in this guideline is framed by a box and presented as shown below: The left column contains the content of the recommendation using the standardized terms/guideline wording; the middle column shows the direction and strength of recommendation with arrows and colored background; and the right column shows the strength of consensus in the guideline committee and the evidence base (consensus-based vs. evidence-based). Consensus strength is classified in Table 2.

TABLE 2 Classification of strength of consensus.

Strong consensus	> 95 %
Consensus	> 75–95 %
Majority Approval	> 50–75 %
No Approval	< 50 %

Example of a recommendation with standardized guideline wording and symbols:

We recommend that …	↑↑	Strong consensus, expert consensus

Consensus procedure

A German translation of the English-language S3 guideline "*The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria*" by Zuberbier et al. (2021)[1] was read by all experts. In an online Delphi procedure, the background texts were pre-approved in sections, and the recommendations item by item. Comments were collected and compiled by the *Methods* group, then referred back to the experts. Amended drafts were then subjected to final discussion and consensus in an online consensus meeting on October 25, 2021, moderated by the AMWF guideline counselor and methodical coordinator Prof. Dr. Alexander Nast. Essentially all recommendations were adopted from the international guideline. Minor deviations in the wording derived from reasons of translation or in cases where the respective recommendation had to be adapted to the

health care setting in Germany (such as the addition of a note on off-label use; please refer to the guideline report for further details).

External review / Approval by the professional societies / Implementation

Both the international S3 guideline and the German-language adaptation were subjected to an extensive external review. In the former case, the review lasted from 21.06.2021 to 31.07.2021 and included various national professional societies as well as the members of the European Dermatology Forum. In the latter case, the review lasted from 01.12.2021 to 17.01.2022 and included the chairpersons from the respective professional societies involved. During both review procedures, the members of the respective guideline committees could submit additional comments.

Final approval for the adapted German-language version was granted after review by the 2+2 committee from the German Dermatological Society and the Professional Society of German Dermatologists. Approval by the boards of the other participating professional societies was given by 31.01.2022.

Dissemination and implementation were conducted within the framework of an existing project of the German Dermatological Society.

Updates / Validity

This guideline is valid until 31.01.2025.

Prof. Dr. Torsten Zuberbier (torsten.zuberbier@charite.de) is the contact person for any updates of the guideline.

Systematic updates of the English-language international guideline are routinely conducted every four years, and the next consensus meeting is planned for December 2024. However, a number of medications are currently being investigated for use in urticaria, and these developments have been discussed during the guideline consensus meeting. Although it is currently too early to issue any recommendations, a review of the guideline after two years is planned to cover any new drug approvals. If this is the case, the respective medications will be discussed in a separate amendment.

MANAGEMENT OF URTICARIA

Basic considerations

The goal of treatment is to treat the disease until it has completely resolved, as efficiently and safely as possible, aiming at a continuous UAS7 = 0, complete control and a normalization of quality of life.

The therapeutic approach to CU should involve

a. the search for and, if possible, elimination of underlying causes, which means healing the disease
b. the avoidance of eliciting factors, reducing disease activity
c. tolerance induction, reducing disease activity
d. the use of pharmacological treatment to prevent mast cell mediator release and/or the effects of mast cell mediators, reducing disease activity

Treatment should follow the basic principles of treating as much as needed and as little as possible, taking into consideration that the activity of the disease may vary. This implies stepping up or stepping down in the treatment algorithm according to the course of disease, following the principle assess, adjust, act, and reassess (Figure 1).

Should treatment aim at complete symptom control in urticaria?

We **recommend** aiming at complete symptom control in urticaria, considering as much as possible the safety and the quality of life of each individual patient.	↑↑	Strong consensus, expert consensus

Identification and elimination of underlying causes and avoidance of eliciting factors

Although desirable, the elimination of underlying causes is not possible in most patients with urticaria. The underlying causes of CIndU are unknown, the underlying causes of acute spontaneous urticaria remain unknown in most patients, and the most common underlying causes of CSU, type I and type Iib autoimmunity, cannot be eliminated. The reduction of autoantibodies by plasmapheresis has been shown to be of temporary benefit in some, severely affected patients with CSU,[4] but experience and evidence are limited and costs are high.

In contrast, the avoidance of triggering factors, where possible, can be of benefit for patients with urticaria.[5] In CIndU, avoidance of specific and definite triggers for the development of signs and symptoms, for example, cold in cold urticaria, can reduce disease activity. In CSU, avoidance of individually relevant and unspecific triggers, for example stress or the intake of NSAIDs, can help to reduce disease exacerbations. Importantly, the avoidance of triggers, in patients with CIndU and in patients with CSU, can result in markedly impaired quality of life, for example in patients with cholinergic urticaria who abstain from physical exercise or in patients with solar urticaria who avoid being outside.

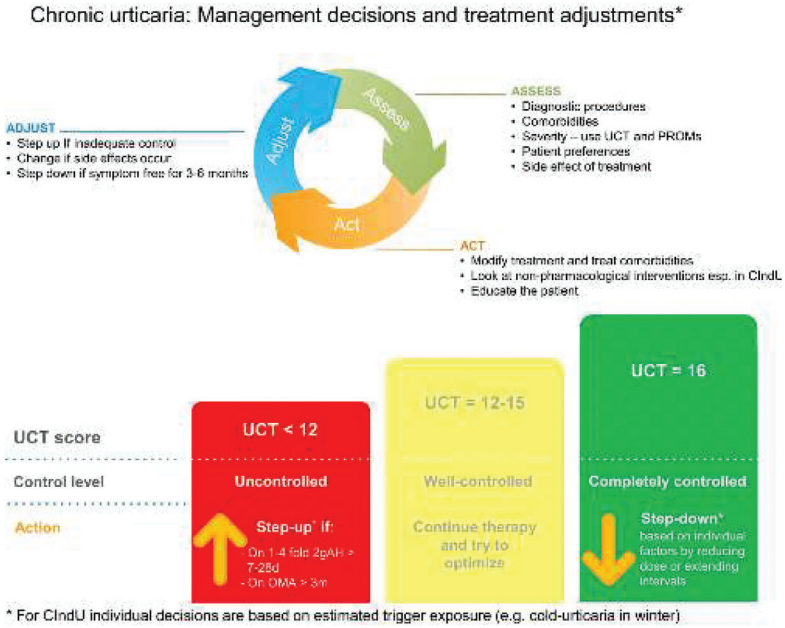

FIGURE 1 Chronic urticaria: Management decisions and treatment adjustments. This Figure was approved with strong consensus during the consensus conference, and all content is consensus-based. *Abbr.* CIndU: chronic inducible urticaria; d: days; m: months; PROMs: patient-reported outcome measures; OMA: omalizumab; 2gAH: 2nd generation H1-antihistamine; UCT: Urticaria Control Test.

Drugs

When these agents are suspected in the course of diagnostic workup, they should be omitted entirely (after consultation with the treating physician, if necessary) or substituted for another class of agents if indispensable. Drugs causing non-allergic hypersensitivity reactions (the prototypes being NSAIDs) cannot only elicit, but can also aggravate[5] preexisting CSU, so that elimination in the latter case will only improve symptoms in some patients.

Should patients with chronic spontaneous urticaria be advised to discontinue medication suspected of aggravating the disease?

We **recommend** advising patients with chronic spontaneous urticaria to discontinue medication that is suspected of aggravating the disease, for example, NSAIDs*.	↑↑	Strong consensus, expert consensus

*Non-steroidal anti-inflammatory drugs such as ibuprofen, diclofenac, aspirin

Definite and specific triggers of CIndU

Avoidance of the specific and definite triggers of CIndUs can help to reduce the occurrence of wheals and angioedema, but usually does not suffice to control the disease and can come with a substantial burden. Patients should be provided with information that helps them to recognize and minimize relevant trigger exposure. Patients with delayed pressure urticaria, for example, should be informed that pressure is defined as force per area and that simple measures, such as broadening of the handle of heavy bags, may be helpful in the prevention of symptoms. Similar considerations hold for cold urticaria where the impact of the wind chill factor in cold winds needs to be remembered. For solar urticaria, accurate determination of the range of eliciting wavelengths may be important for the appropriate selection of sunscreens or for the selection of light bulbs with an UV-A filter. However, in many patients, the threshold for the relevant physical trigger is low and total avoidance of symptoms is virtually impossible. For example, severe symptomatic dermographism is sometimes confused with CSU because seemingly spontaneous hives are observed where even loose-fitting clothing rubs on the patient's skin or unintentional scratching by patients readily causes the development of wheals in that area.

Infections and inflammatory processes

In contrast to CIndU, CSU has been reported to be associated with a variety of inflammatory or infectious diseases. This is regarded as significant in some instances, but studies show conflicting results and have methodological weaknesses. Infections that may contribute to CSU disease activity include those of the gastrointestinal tract like *H. pylori* infection[6] and bacterial infections of the nasopharynx as well as the teeth and the periodontium.[7] Even if association with urticaria is not clear in the individual patient and a meta-analysis shows overall low evidence for eradication therapy, *H. pylori* should be eliminated, as an association with gastric cancer has been suggested.[8] A recent meta-analysis has shown moderate evidence for remission and symptom relief in urticaria after eradication of *H. Pylori*, with good tolerability.[9]

Bowel parasites, a rare possible cause of CSU in developed industrial countries, should be eliminated

if indicated.[6,10] In the past, intestinal candidiasis was regarded as a very important underlying cause of CSU,[6] but more recent findings fail to support a significant causative role.[11] Apart from infectious diseases, chronic inflammatory processes due to diverse other diseases have been identified as potentially triggering CSU. These can be secondary to infections. This holds particularly for gastritis, reflux esophagitis, or inflammation of the bile duct or gall bladder.[12,13] Thus, it could be shown that the successful eradication of helicobacter only has an impact on CSU if the subsequent inflammation, that is, gastritis and esophagitis is also healed.[14] However, similar to infections, it is not easily possible to discern whether any of these are relevant causes of CSU, although they should be treated anyway as many of them may also be associated with development of malignancies.

A connection between CsU and chronic or recurrent acute tonsillitis cannot usually be deducted based on the assumption of an inflammatory focus in dermatological disease. There is no sufficient evidence for such an assumption.

Only in individual cases of frequent and repeated direct temporal connections between recurrent acute tonsillitis and respective dermatological symptoms may a causative connection be suspected. This suspicion should be discussed between the dermatologist and the ENT specialist. Morbidity needs to be considered in view of possible life-threatening hemorrhage after tonsillectomy.[15–17]

Stress

Although the mechanisms of stress-induced exacerbation are not well investigated, some evidence indicates that disease activity in patients with CSU can be linked to stress.[18,19] Further studies are needed to characterize the prevalence and relevance of CSU exacerbation by stress as well as the underlying mechanisms.

Reduction of functional autoantibodies

Direct reduction of functional autoantibodies by plasmapheresis has been shown to be of temporary benefit in some severely affected patients.[4] Due to limited experience and high costs, this therapy is suggested for autoantibody-positive CSU patients who are unresponsive to all other forms of treatment. Autoantibodies and potentially activated T cells may also be reduced by immunosuppressive medication, such as cicloporin.[20]

Food

IgE-mediated food allergy is extremely rarely the underlying cause of CSU.[12,21] If identified, the specific food allergens need to be omitted as much as possible, which leads to a remission within less than 24 h. In some CSU patients, pseudoallergic reactions (non-IgE-mediated hypersensitivity reactions) to naturally occurring food ingredients and in some cases to food additives have been observed.[12,21–25] A pseudoallergen-free diet, containing only low levels of natural and artificial food pseudoallergens, has been tested in different countries,[26] and a low histamine diet may also improve symptoms in some patients. [27]

Evidence for these diets is controversial since there are many open studies with favorable results, but naturally the 'gold standard' of double-blinded placebo-controlled studies cannot be achieved. When used they must usually be maintained for a minimum of 2–3 weeks before beneficial effects are observed. This kind of treatment requires cooperative patients, and success rates may vary considerably due to regional differences in food and dietary habits. More research is necessary on the effects of natural and artificial ingredients of food on urticaria.

Inducing tolerance

Inducing tolerance can be useful in some subtypes of CIndU. Examples are cold urticaria, cholinergic urticaria, and solar urticaria, where a rush therapy with UV-A has been reported to be effective within 3 days.[28] However, tolerance induction only lasts a few days; thus, a consistent daily exposure to the stimulus at the current threshold level is required.

Tolerance induction and maintenance are often not accepted by patients, for example, in the case of cold urticaria where daily cold baths/showers are needed to achieve this.

Detailed information is essential to improve acceptance. In the case of regular UV-A exposure, the possible risks of this type of radiation need to be considered as well, so the measure can only be implemented for short periods of time.

Symptomatic pharmacological treatment

The targets and aims of pharmacological therapies and the need for continued treatment

Current recommended treatment options for urticaria aim to target mast cell mediators such as histamine, or activators such as autoantibodies. Novel treatments currently under development aim to silence mast cells via inhibitory receptors or to reduce mast cell numbers. The overall goal of all these symptomatic treatments is to help patients be free of signs and symptoms until their urticaria shows spontaneous remission. To achieve this, pharmacological treatment should be continuous, until no longer needed. Non-sedating 2nd generation H1-antihistamines, for example, should be used daily, to prevent the occurrence of wheals and angioedema, rather than on demand. This is supported by their safety profile (safety data are available

for several years of continuous use), the results of randomized controlled trials and real-life studies,[29,30] and their mechanism of action, that is, their inverse agonist effects on the H1 receptor, stabilizing its inactive state. Some patients with CIndU can benefit from short-term prophylactic antihistamine treatment before relevant trigger exposure.

Treatment with second-generation H_1 antihistamines

H1-antihistamines have been available for the treatment of urticaria since the 1950s. The older 1st generation H1-antihistamines have pronounced anticholinergic and sedative effects, and many interactions with alcohol and other drugs, such as analgesics, hypnotics, sedatives, and mood-elevating drugs, have been described. They can also interfere with rapid eye movement (REM) sleep and impact on learning and performance. Impairment is particularly prominent during multi-tasking and performance of complex sensorimotor tasks such as driving. In a GA^{2}LEN position paper,[31] it is strongly recommended that 1st generation H1-antihistamines no longer be used in allergy both for adults and especially in children. This view is shared by the WHO guideline ARIA.[32] Based on strong evidence regarding potentially serious side effects of 1st generation H1-antihistamines (lethal overdoses have been reported), we recommend against their use for the routine management of CU as first-line agents.

Modern 2nd generation H1-antihistamines are minimally or non-sedating and free of anticholinergic effects.[33] However, two 2nd generation H1-antihistamines, astemizole and terfenadine, are shown to have cardiotoxic effects in patients treated with inhibitors of the cytochrome P450 (CYP) 3A4 isoenzyme, such as ketoconazole or erythromycin. Astemizole and terfenadine are no longer available in most countries, and we recommend that they are not used.

Most but not all 2nd generation H1-antihistamines have been tested specifically in urticaria, and evidence supports the use of bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, and rupatadine. We recommend the use of a standard-dosed modern 2nd generation H1-antihistamine as the first-line symptomatic treatment for urticaria. However, no recommendation can be made on which to choose because, to date, well-designed clinical trials comparing the efficacy and safety of all modern 2nd generation H1-antihistamines in urticaria are largely lacking.

Should modern 2nd generation H1-antihistamines be used as first-line treatment of urticaria?

We **recommend** a 2nd generation H1-antihistamine as first-line treatment for all types of urticaria.	↑↑	Strong consensus, evidence- and consensus-based (online supplement 1, p. 4–9, p. 10–18)

Is an increase in the dose to up to fourfold of modern 2nd generation H1-antihistamines useful and to be preferred over other treatments in urticaria?

We **recommend** updosing of a 2nd generation H1-antihistamine up to fourfold in patients with chronic urticaria unresponsive to a standard-dosed 2nd generation H1-antihistamines as second-line treatment before other treatments are considered.	↑↑	Strong consensus, evidence- and consensus-based (online supplement 1, pp. 24–31)

Should modern 2nd generation H1-antihistamines be taken regularly or as needed?

We **suggest** 2nd generation H1-antihistamines to be taken regularly for the treatment of patients with chronic urticaria.	↑	Strong consensus, evidence- and consensus-based (online supplement 1, pp. 18–20)

Should different 2nd generation H1-antihistamines be used at the same time?

We **suggest against** using different H1-antihistamines at the same time.	↓	Strong consensus, evidence- and consensus-based (online supplement 1, pp. 21–23)

Several studies have shown the benefit of the use of a higher than standard-dosed 2nd generation H1-antihistamine in urticaria patients,[34–36] corroborating earlier studies with 1st generation H1-antihistamines that came to the same conclusion.[37,38] Studies support the (off-label) use of up to four times the standard dose of bilastine, cetirizine, desloratadine, ebastine (40 mg per day at most), fexofenadine, levocetirizine, and rupatadine.[34,35,39–42]

In summary, these studies suggest that some patients with urticaria, who show insufficient response to a standard-dosed 2nd generation H1-antihistamine, benefit from updosing which is preferred over mixing different 2nd generation H1-antihistamines as their pharmacologic properties are different. We therefore recommend increasing the dose up to four times the standard age-adjusted dose in such patients (Figure 2). Patients need to be informed that 2nd generation H1-antihistamine updosing is off-label. However, updosing has been suggested in the guidelines for urticaria since 2000, and so far no serious adverse events have been reported, nor has a side effect ever been reported in the literature attributed to long-term intake and potential accumulation. Dosages higher than fourfold are not recommended as this has not been tested.

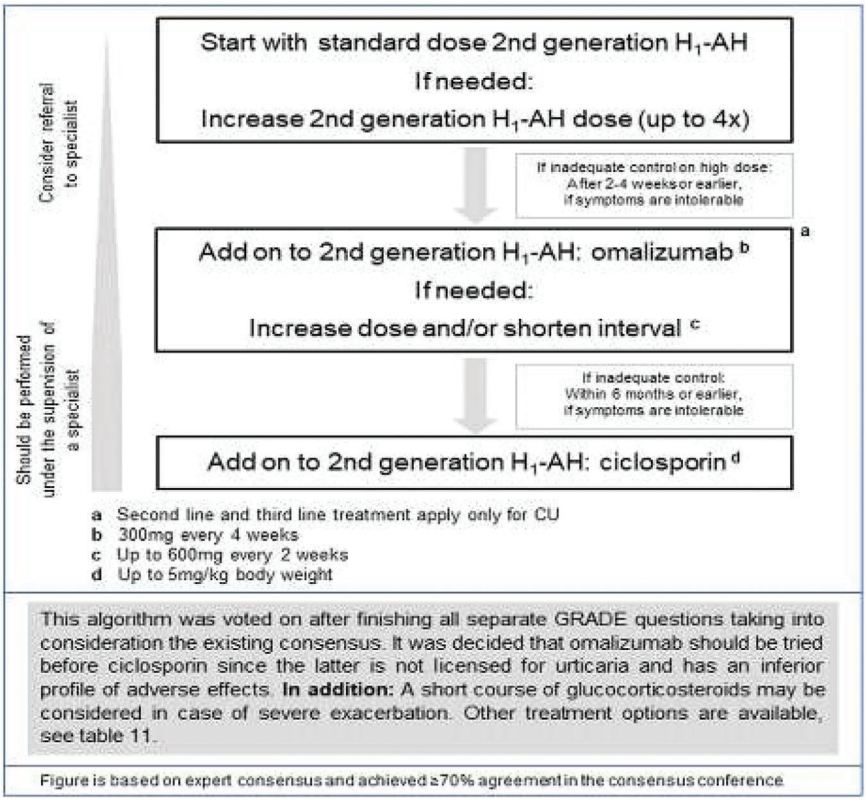

FIGURE 2 Recommended treatment algorithm for urticaria. This Figure was approved with strong consensus during the consensus conference, and all content is consensus-based. AH, antihistamine; CU, chronic urticaria; GRADE, Grading of Recommendations Assessment, Development and Evaluation (working group). *First line* = High quality evidence: Low cost and worldwide availability (e.g. modern 2nd generation H1-antihistamines exist also in developing countries mostly cheaper than old sedating antihistamines), per daily dose as the half life time is much longer, very good safety profile, good efficacy. *Second line* (omalizumab as add on to 2nd generation H1-antihistamine) = High quality evidence: High cost, very good safety profile, very good efficacy. *Third line* (ciclosporin as add on) = High quality evidence: Medium to high cost, moderate safety profile, good efficacy. Short course of corticosteroids = Low quality evidence: Low cost, worldwide availability, good safety profile (for short course only), good efficacy during intake, but not suitable for long term therapy.

If there is no improvement, should higher than fourfold doses of 2nd generation H1-antihistamines be used?

We **recommend against** using higher than fourfold standard-dosed H1-antihistamines in chronic urticaria	↓↓	Strong consensus, evidence- and consensus-based (online supplement 1, p. 32)

Omalizumab treatment

Omalizumab is the only other licensed treatment for urticaria in patients who do not show sufficient benefit from treatment with a 2nd generation H1-antihistamine, and is therefore the next step in the algorithm. Omalizumab (anti-IgE) has been shown to be very effective and safe in the treatment of CSU.[43–48] Omalizumab has also been reported to be effective in CindU,[49,50] including cholinergic urticaria,[51] cold urticaria,[52,53] solar urticaria,[54] heat urticaria,[55] symptomatic dermographism,[56,57] and delayed pressure urticaria.[58] In CSU, omalizumab prevents wheal and angioedema development,[59] markedly improves quality of life,[60,61] is suitable for long-term treatment,[58] and effectively treats relapse after discontinuation.[58,62] The recommended initial dose in CSU is 300 mg every 4 weeks. Dosing is independent of total serum IgE.[63]

Patients with urticaria who do not show sufficient benefit from treatment with omalizumab at the licensed dose of 300 mg every 4 weeks can be treated with omalizumab at higher doses, shorter intervals, or both. Studies support the use of omalizumab treatment at doses up to 600 mg and intervals of 2 weeks, in patients with insufficient response to standard-dosed omalizumab. Patients need to be informed that omalizumab updosing either by increasing the dose or by shortening the intervals is off-label. Reimbursement needs to be confirmed in advance by the patient's health insurance after an application has been submitted accordingly.

Is omalizumab useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines?

We **recommend** adding on omalizumab* for the treatment of patients with CU unresponsive to high dose 2nd generation H1-antihistamines. **currently licensed for chronic spontaneous urticaria*	↑↑	Strong consensus, evidence- and consensus-based (online supplement 1, pp. 33-41)

Ciclosporin treatment

Patients with urticaria who do not show sufficient benefit from treatment with omalizumab should be treated with ciclosporin (cyclosporin A; CSA) 3.5–5 mg/kg per day. Ciclosporin is immunosuppressive and has a moderate,

direct effect on mast cell mediator release.[64,65] Efficacy of ciclosporin in combination with a modern 2nd generation H1-antihistamine has been shown in placebo-controlled trials[20,66,67] as well as open controlled trials[66] in CSU, but this drug cannot be recommended as standard treatment due to a higher incidence of adverse effects.[66] Ciclosporin is off-label for urticaria and is recommended only for patients with severe disease refractory to any dose of antihistamine and omalizumab in combination (Figure 2). Again, patients need to be informed that this use of CSA is off-label. Reimbursement needs to be confirmed in advance by the patient's health insurance after an application has been submitted accordingly. However, CSA has a far better risk/benefit ratio compared with long-term use of steroids. In patients with hypertension or renal failure, CSA should either not be used at all, or only after a thorough risk-benefit assessment.

Is ciclosporin (CSA) useful as add-on treatment in patients unresponsive to high doses of H1-antihistamine?

We **suggest** using ciclosporin for the treatment of patients with CU unresponsive to high dose of 2nd generation H1-antihistamine and omalizumab.	↑	Strong consensus, evidence- and consensus-based (online supplement 1, pp. 42-44)

Other symptomatic treatments

Some previous randomized controlled trials (RCT) have assessed the use of leukotriene receptor antagonists. The studies are difficult to compare due to the different populations examined. For example, cohorts may include only aspirin and food additive intolerant patients or may exclude ASST-positive patients. In general, the level of evidence for the efficacy of leukotriene receptor antagonists in urticaria is low, the best being for montelukast.

At present, topical corticosteroids are frequently and successfully used in many allergic diseases, but in urticaria topical steroids are not helpful (with the possible exception of pressure urticaria on the soles of the feet as an alternative therapy with low evidence). If systemic corticosteroids are used, doses between 20 and 50 mg/d of prednisone equivalent are needed (dose is appropriate for adults and not children). Because such high doses will have side effects over the long term, we strongly recommend against the use of corticosteroids outside of specialist clinics. Depending on the country, it must be noted that steroids are also not licensed for CU (for example, in Germany prednisolone is only licensed for acute urticaria). However, for acute urticaria and acute exacerbations of CSU, a short course of oral corticosteroids, that is, treatment for a maximum of up to 10 days, may be helpful in reducing disease duration/activity.[68,69] Nevertheless, well-designed RCTs are lacking.

Should oral corticosteroids be used as add-on treatment in the treatment of urticaria?

We **recommend against** the long-term use of systemic glucocorticosteroids in CU.	↓↓	Strong consensus, evidence- and consensus-based (online supplement 1, p. 50)

While antihistamines at up to quadruple the manufacturers' recommended dosages will control symptoms in a large proportion of patients with urticaria in general practice, alternative treatments are needed for the remaining unresponsive patients. It is strongly recommended that the algorithm be followed, even though the guideline committee acknowledges that the use of omalizumab and ciclosporin are subject to limitations due to the high cost and safety profile, respectively.

Since the severity of urticaria may fluctuate, and spontaneous remission may occur at any time, it is also recommended to re-evaluate the necessity for continued or alternative drug treatment every 3–6 months. This is also illustrated in Figure 1.

All treatments not listed in the treatment algorithm (Figure 2) are based on clinical trials with low levels of evidence (Table 3).

H_2-antagonists and dapsone, recommended in the previous versions of the guideline, are now perceived as having too little evidence to warrant renewed inclusion in the algorithm. Sulfasalazine, methotrexate, interferon, plasmapheresis, phototherapy, intravenous immunoglobulins (IVIG/IGIV), and other treatment options have low-quality evidence or have only been described in case series[70] (Table 3). Despite the lack of published evidence, all these drugs may still be of value to individual patients in the appropriate clinical context,[71] after detailed information on potential side effects has been provided.

Are H2-antihistamines useful as add-on treatment in patients unresponsive to low or high doses of H1-antihistamines?

We **cannot make a recommendation** for or against the combined use of H1- and H2-antihistamines in patients with chronic urticaria.	0	Strong consensus, expert consensus

Antagonists of tumor necrosis factor alpha (TNF-alpha)[72] and IVIG/IGIV,[73–76] which have been successfully used in case reports, are currently only recommended to be used in specialized centers as a last option (that is, anti-TNF-alpha for delayed pressure urticaria and IVIG/IGIV for CSU).[77,78]

For the treatment of CSU and symptomatic dermographism, UV-B (narrow band-UVB, TL01), UV-A, and PUVA treatment for 1–3 months can be added to antihistamine treatment,[79–81] but caution is advised regarding the carcinogenic properties of UV light treatment.

TABLE 3 Alternative treatment options. Although evidence from publications is low, clinical experience indicates that they may be useful in certain contexts. Interventions are listed in alphabetical order by frequency of use rather than efficacy.

Widely used		
Antidepressant	Doxepin*	CSU
Diet	Pseudoallergen-free diet**	CSU
H2-antihistamine	Ranitidine***	CSU
Immunosuppressive	Methotrexate^Mycophenolate mofetil	CSU +/– DPU**** Autoimmune CSU
Leukotriene receptor antagonist	Montelukast	CSU, DPU
Sulphones	Dapsone, Sulphasalazine	CSU +/– DPU CSU +/– DPU
Infrequently used		
Anabolic steroid	Danazol	Cholinergic urticaria
Anticoagulant	Warfarin	CSU
Antifibrinolytic	Tranexamic acid	CSU with angioedema
Immunomodulator	IVIG^Plasmapheresis	Autoimmune CSU Autoimmune CSU
Miscellaneous	Autologous blood/serum Hydroxychloroquine	CSU CSU
Phototherapy	Narrow-band UVB	Symptomatic dermographism
Psychotherapy	Holistic medicine	CSU
Rarely used		
Anticoagulant	Heparin	CSU
Immunosuppressive	Cyclophosphamide Rituximab	Autoimmune CSU Autoimmune CSU
Miscellaneous	Anakinra	DPU
	Anti-TNF-alpha	CSU +/– DPU
	Camostat mesilate	CSU
	Colchicine	CSU
	Miltefosine	CSU
	Mirtazepine	CSU
	PUVA	CSU
Very rarely used		
Immunosuppressive	Tacrolimus	CSU
Miscellaneous	Vitamin D	CSU
	Interferon alpha	CSU

Abbr.: CSU, chronic spontaneous urticaria; IVIG, intravenous immunoglobulins; PUVA, Psoralen plus UV-A or photochemotherapy; TNFα, Tumor necrosis factor alpha; UV-B, Ultraviolet-B; DPU, delayed pressure urticaria

*Has also H1 and H2-antihistaminergic properties.

**Does include low histamine diet as pseudoallergen-free diet is also low in histamine.

***No longer available in most countries; alternative H2-antihistamines are available including famotidine and nizatidine but evidence for their use in chronic urticaria varies.

****Treatment can be considered especially if CSU and DPU are co-existent in a patient.

Some treatment alternatives formerly proposed have been shown to be ineffective in double-blind, placebo-controlled studies and should no longer be used, as the grade of recommendation is low. These include tranexamic acid and sodium cromoglycate in CSU,[82,83] nifedipine in symptomatic dermographism/urticaria factitia[84] and colchicine and indomethacin in delayed pressure urticaria.[85,86] However, more research may be needed for patient subgroups; for example, a pilot study[87] of patients with elevated D-dimer levels showed that heparin and tranexamic acid therapy may be effective.

Could any other treatment options be recommended for the treatment of urticaria?

We **cannot make a recommendation** with respect to further treatment options as standard therapies, but these may be considered in special cases, which also include those where financial or legal limitations for the recommended algorithm treatment exist.	0	Strong consensus, expert consensus

Treatment of special populations

Children

Many clinicians use 1st generation H1-antihistamines as a first-choice treatment for children with urticaria, with the assumption that their safety profile is better known than that of the modern 2nd generation H1-antihistamines, due to a longer experience with them. Also, the use of modern 2nd generation H1-antihistamines is not licensed for use in children under 6 months of age in many countries. However, 1st generation H1-antihistamines have an inferior safety profile compared with 2nd generation H1-antihistamines, and are, therefore, not recommended as first-line treatment in children with urticaria. 2nd generation H1-antihistamines with proven efficacy and safety in the pediatric population include bilastine,[88] cetirizine,[89] desloratadine,[90,91] fexofenadine,[92] levocetirizine,[93] loratadine,[89] and rupatadine.[94] The choice of which 2nd generation H1-antihistamines to use in children with urticaria should take into consideration the age of the child and available dosage forms, as not all are available as syrup or fast dissolving tablets suitable for children. The lowest licensed age also differs from country to country, and if applicable, parents should be informed about off-label use. All further steps should be based on individual considerations and be taken carefully, as updosing of antihistamines and further treatment options are not well studied in children.

Should the same treatment algorithm be used in children?

We **suggest** using the same treatment algorithm with caution (for example, weight-adjusted dosage) in children with chronic urticaria	↑	Strong consensus, expert consensus

Pregnant and lactating women

The same considerations in principle apply to pregnant and lactating women. In general, use of any systemic treatment should be avoided in pregnant women, especially in the first trimester. On the other hand, pregnant women have a right to receive the best therapy possible. While the safety of treatment has not been systematically studied in pregnant women with urticaria, it should be pointed out that the possible negative effects of increased levels of histamine receptor binding occurring in urticaria have also not been studied during pregnancy. Regarding treatment, no reports of birth defects in women having used modern 2nd generation H1-antihistamines during pregnancy have been reported to date. However, only small sample size studies are available for cetirizine[95] and one large meta-analysis for loratadine.[96] Furthermore, as several modern 2nd generation H1-antihistamines are now prescription free and used widely in both allergic rhinitis and urticaria, it must be assumed that many women have used these drugs especially at the beginning of pregnancy, or at least before the pregnancy was confirmed. Nevertheless, since the highest safety is mandatory in pregnancy, the suggestion for the use of modern 2nd generation H1-antihistamines is to prefer loratadine with the possible extrapolation to desloratadine, and cetirizine with a possible extrapolation to levocetirizine. All H1-antihistamines are excreted in breast milk in low concentrations. Use of 2nd generation H1-antihistamines is advised, as nursing infants occasionally develop sedation from the old 1st generation H1-antihistamines excreted in breast milk.

The increased dosage of modern 2nd generation H1-antihistamines in pregnancy can only be recommended with caution, since no safety studies are available. For loratadine, it must be remembered that the drug is metabolized in the liver, while this is probably not the case for its metabolite desloratadine. 1st generation H1-antihistamines should be avoided.[31] The use of omalizumab in pregnancy has been reported to be safe, and to date, there is no indication of teratogenicity.[97–99] All further steps should be based on individual considerations, with a preference for medications that have a satisfactory risk-to-benefit ratio in pregnant women and neonates with regard to teratogenicity and embryotoxicity. For example, ciclosporin, although not teratogenic, is embryotoxic in animal models and is associated with preterm delivery and low birth weight in human infants. Whether the benefits of ciclosporin in CU are worth the risks in pregnant women must be determined on a case-by-case basis. However, all decisions should be re-evaluated according to the current recommendations published by regulatory authorities.

Should the same treatment algorithm be used in pregnant women and during lactation?

We **suggest** using the same treatment algorithm with caution both in pregnant and lactating women after risk-benefit assessment. Drugs contraindicated or not suitable in pregnancy should not be used.	↑	Strong consensus, expert consensus

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REFERENCES

1. Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al. The international EAACI/GA(2)LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. 2022;77:734-766.
2. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines:1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64:383-394.
3. Kaminski-Hartenthaler A, Meerpohl JJ, Gartlehner G, et al. GRADE guidelines:14. Going from evidence to recommendations: the

significance and presentation of recommendations. *Z Evid Fortbild Qual Gesundhwes*. 2014;108:413-420.
4. Grattan CE, Francis DM, Slater NG, et al. Plasmapheresis for severe, unremitting, chronic urticaria. *Lancet*. 1992;339:1078-1080.
5. Kowalski ML, Woessner K, Sanak M. Approaches to the diagnosis and management of patients with a history of nonsteroidal anti-inflammatory drug-related urticaria and angioedema. *J Allergy Clin Immunol*. 2015;136:245-251.
6. Shakouri A, Compalati E, Lang DM, Khan DA. Effectiveness of *Helicobacter pylori* eradication in chronic urticaria:evidence-based analysis using the Grading of Recommendations Assessment, Development, and Evaluation system. *Curr Opin Allergy Clin Immunol*. 2010;10:362-369.
7. Wedi B, Raap U, Wieczorek D, Kapp A. Urticaria and infections. *Allergy Asthma Clin Immunol*. 2009;5:10.
8. Ishaq S, Nunn L. *Helicobacter pylori* and gastric cancer:a state of the art review. *Gastroenterol Hepatol Bed Bench*. 2015;8:S6-S14.
9. Watanabe J, Shimamoto J, Kotani K. The effects of antibiotics for *Helicobacter pylori* eradication or dapsone on chronic spontaneous urticaria: a systematic review and meta-analysis. *Antibiotics (Basel)*. 2021;10:156.
10. Henz BM ZT, Grabbe J, Monroe E. Urticaria. Clinical, diagnostic and therapeutic aspects. In: *Causes of urticaria*. Springer, 1998.
11. Ergon MC, ilknur T, Yucesoy M, Ozkan S. Candida spp. colonization and serum anticandidal antibody levels in patients with chronic urticaria. *Clin Exp Dermatol*. 2007;32:740-743.
12. Zuberbier T, Chantraine-Hess S, Hartmann K, Czarnetzki BM. Pseudoallergen-free diet in the treatment of chronic urticaria. A prospective study. *Acta Derm Venereol*. 1995;75:484-487.
13. Bruno G, Andreozzi P, Graf U. Exercise-induced urticaria-angioedema syndrome:A role in gastroesophageal reflux. In: Vena G. A. PP:Proceedings of the international symposium on urticaria.: Bari. Editrice CSH, Milan, 1998:85-89.
14. Zheleznov S, Urzhumtseva G, Petrova N, et al. Gastritis can cause and trigger chronic spontaneous urticaria independent of the presence of *Helicobacter pylori*. *Int Arch Allergy Immunol*. 2018;175:246-251.
15. Stuck BA, Gotte K, Windfuhr JP, et al. Tonsillectomy in children. *Dtsch Arztebl Int*. 2008;105:852-860;quiz 60–61.
16. Müller A, Neuber K, Metternich FU, Wenzel S. Effekt der Fokus-Tonsillektomie bei chronischen Dermatosen – Klinische Studie und Metaanalyse. *Laryngorhinootologie*. 2004;83:26-12.
17. Schulze W. *Tonsillektomie zur Fokussanierung bei der Psoriasis, der atopischen Dermatitis und der chronischen Urtikaria*. Staats-und Universitätsbibliothek Hamburg Carl von Ossietzky, 2012.
18. Varghese R, Rajappa M, Chandrashekar L, et al. Association among stress, hypocortisolism, systemic inflammation, and disease severity in chronic urticaria. *Ann Allergy Asthma Immunol*. 2016;116:344-348.e1.
19. Schut C, Magerl M, Hawro T, et al. Disease activity and stress are linked in a subpopulation of chronic spontaneous urticaria patients. *Allergy*. 2020;75:224-226.
20. Grattan CE, O'Donnell BF, Francis DM, et al. Randomized double-blind study of cyclosporin in chronic „idiopathic" urticaria. *Br J Dermatol*. 2000;143:365-372.
21. Juhlin L. Recurrent urticaria:clinical investigation of 330 patients. *Br J Dermatol*. 1981;104:369-381.
22. Pfrommer C, Bastl R, Vieths S, et al. Characterization of naturally occurring pseudoallergens causing chronic urticaria. *J Allergy Clin Immunol*. 1996;97:367.
23. Pigatto PD, Valsecchi RH. Chronic urticaria:a mystery. *Allergy*. 2000;55:306-308.
24. Bunselmeyer B, Laubach HJ, Schiller M, et al. Incremental build-up food challenge – a new diagnostic approach to evaluate pseudoallergic reactions in chronic urticaria:a pilot study:stepwise food challenge in chronic urticaria. *Clin Exp Allergy*. 2009;39:116-126.
25. Nettis E, Colanardi MC, Ferrannini A, Tursi A. Sodium benzoate-induced repeated episodes of acute urticaria/angioedema:randomized controlled trial. *Br J Dermatol*. 2004;151:898-902.
26. Akoglu G, Atakan N, Cakir B, et al. Effects of low pseudoallergen diet on urticarial activity and leukotriene levels in chronic urticaria. *Arch Dermatol Res*. 2012;304:257-262.
27. Wagner N, Dirk D, Peveling-Oberhag A, et al. A Popular myth – low-histamine diet improves chronic spontaneous urticaria - fact or fiction? *J Eur Acad Dermatol Venereol*. 2017;31:650-655.
28. Beissert S, Stander H, Schwarz T. UVA rush hardening for the treatment of solar urticaria. *J Am Acad Dermatol*. 2000;42:1030-1032.
29. Grob JJ, Auquier P, Dreyfus I, Ortonne JP. How to prescribe antihistamines for chronic idiopathic urticaria:desloratadine daily vs PRN and quality of life. *Allergy*. 2009;64:605-612.
30. Weller K, Ardelean E, Scholz E, et al. Can on-demand non-sedating antihistamines improve urticaria symptoms? A double-blind, randomized, single-dose study. *Acta Derm Venereol*. 2013;93:168-174.
31. Church MK, Maurer M, Simons FE, et al. Risk of first-generation H(1)-antihistamines:a GA(2)LEN position paper. *Allergy*. 2010;65:459-466.
32. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63(Suppl 86):8-160.
33. Kubo N, Senda M, Ohsumi Y, et al. Brain histamine H1 receptor occupancy of loratadine measured by positron emission topography:comparison of H1 receptor occupancy and proportional impairment ratio. *Hum Psychopharmacol*. 2011;26:133-139.
34. Kontou-Fili K, Paleologos G, Herakleous M. Suppression of histamine-induced skin reactions by loratadine and cetirizine diHCl. *Eur J Clin Pharmacol*. 1989;36:617-619.
35. Zuberbier T, Munzberger C, Haustein U, et al. Double-blind crossover study of high-dose cetirizine in cholinergic urticaria. *Dermatology*. 1996;193:324-327.
36. Kontou-Fili K, Maniakatou G, Demaka P, Paleologos G. Therapeutic effect of cetirizine 2 HCl in delayed pressure urticaria. *Health Sci Rev*. 1989;3:23-25.
37. Wanderer AA, Ellis EF. Treatment of cold urticaria with cyproheptadine. *J Allergy Clin Immunol*. 1971;48:366-371.
38. Kaplan AP, Gray L, Shaff RE, et al. In vivo studies of mediator release in cold urticaria and cholinergic urticaria. *J Allergy Clin Immunol*. 1975;55:394-402.
39. Staevska M, Popov TA, Kralimarkova T, et al. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. *J Allergy Clin Immunol*. 2010;125:676-682.
40. Siebenhaar F, Degener F, Zuberbier T, et al. High-dose desloratadine decreases wheal volume and improves cold provocation thresholds compared with standard-dose treatment in patients with acquired cold urticaria:a randomized, placebo-controlled, crossover study. *J Allergy Clin Immunol*. 2009;123:672-679.
41. Gimenez-Arnau A, Izquierdo I, Maurer M. The use of a responder analysis to identify clinically meaningful differences in chronic urticaria patients following placebo- controlled treatment with rupatadine 10 and 20 mg. *J Eur Acad Dermatol Venereol*. 2009;23:1088-1091.
42. Guillen-Aguinaga S, Jauregui Presa I, Aguinaga-Ontoso E, et al. Updosing nonsedating antihistamines in patients with chronic spontaneous urticaria:a systematic review and meta-analysis. *Br J Dermatol*. 2016;175:1153-1165.
43. Saini S, Rosen KE, Hsieh HJ, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol*. 2011;128:567-573e1.
44. Maurer M, Altrichter S, Bieber T, et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol*. 2011;128:202-209.e5.
45. Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous

urticaria who remain symptomatic on H1 antihistamines:a randomized, placebo-controlled study. *J Invest Dermatol*. 2015;135:67-75.
46. Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368:924-935.
47. Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol*. 2013;132:101-109.
48. Zhao ZT, Ji CM, Yu WJ, et al. Omalizumab for the treatment of chronic spontaneous urticaria:A meta-analysis of randomized clinical trials. *J Allergy Clin Immunol*. 2016;137:1742-1750.e4.
49. Maurer M, Metz M, Brehler R, et al. Omalizumab treatment in patients with chronic inducible urticaria:A systematic review of published evidence. *J Allergy Clin Immunol*. 2018;141:638-649.
50. Metz M, Altrichter S, Ardelean E, et al. Anti-immunoglobulin E treatment of patients with recalcitrant physical urticaria. *Int Arch Allergy Immunol*. 2011;154:177-180.
51. Metz M, Bergmann P, Zuberbier T, Maurer M. Successful treatment of cholinergic urticaria with anti-immunoglobulin E therapy. *Allergy*. 2008;63:247-249.
52. Boyce JA. Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE. *J Allergy Clin Immunol*. 2006;117:1415-1418.
53. Metz M, Schutz A, Weller K, et al. Omalizumab is effective in cold urticaria-results of a randomized placebo-controlled trial. *J Allergy Clin Immunol*. 2017;140:864-867.e5.
54. Guzelbey O, Ardelean E, Magerl M, et al. Successful treatment of solar urticaria with anti-immunoglobulin E therapy. *Allergy*. 2008;63:1563-1565.
55. Bullerkotte U, Wieczorek D, Kapp A, Wedi B. Effective treatment of refractory severe heat urticaria with omalizumab. *Allergy*. 2010;65:931-932.
56. Krause K, Ardelean E, Kessler B, et al. Antihistamine-resistant urticaria factitia successfully treated with anti-immunoglobulin E therapy. *Allergy*. 2010;65:1494-1495.
57. Maurer M, Schutz A, Weller K, et al. Omalizumab is effective in symptomatic dermographism-results of a randomized placebo-controlled trial. *J Allergy Clin Immunol*. 2017;140:870-873.e5.
58. Maurer M, Kaplan A, Rosén K, et al. The XTEND-CIU study:Long-term use of omalizumab in chronic idiopathic urticaria. *J Allergy Clin Immunol*. 2018;141(3):1138-1139.e7.
59. Staubach P, Metz M, Chapman-Rothe N, et al. Effect of omalizumab on angioedema in H1 -antihistamine-resistant chronic spontaneous urticaria patients:results from X-ACT, a randomized controlled trial. *Allergy*. 2016;71:1135-1144.
60. Finlay AY, Kaplan AP, Beck LA, et al. Omalizumab substantially improves dermatology-related quality of life in patients with chronic spontaneous urticaria. *J Eur Acad Dermatol Venereol*. 2017;31:1715-1721.
61. Maurer M, Sofen H, Ortiz B, et al. Positive impact of omalizumab on angioedema and quality of life in patients with refractory chronic idiopathic/spontaneous urticaria:analyses according to the presence or absence of angioedema. *J Eur Acad Dermatol Venereol*. 2017;31:1056-1063.
62. Metz M, Ohanyan T, Church MK, Maurer M. Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria. *JAMA Dermatol*. 2014;150:288-290.
63. Saini S, Rosen KE, Hsieh HJ, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H-1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol*. 2011;128(3):567-573.e1.
64. Stellato C, de Paulis A, Ciccarelli A, et al. Anti-inflammatory effect of cyclosporin A on human skin mast cells. *J Invest Dermatol*. 1992;98:800-804.
65. Harrison CA, Bastan R, Peirce MJ, et al. Role of calcineurin in the regulation of human lung mast cell and basophil function by cyclosporine and FK506. *Br J Pharmacol*. 2007;150:509-518.
66. Vena GA, Cassano N, Colombo D, et al. Cyclosporine in chronic idiopathic urticaria:a double-blind, randomized, placebo-controlled trial. *J Am Acad Dermatol*. 2006;55:705-709.
67. Kulthanan K, Chaweekulrat P, Komoltri C, et al. Cyclosporine for chronic spontaneous urticaria:a meta-analysis and systematic review. *J Allergy Clin Immunol Pract*. 2018;6:586-599.
68. Zuberbier T, Ifflander J, Semmler C, Henz BM. Acute urticaria:clinical aspects and therapeutic responsiveness. *Acta Derm Venereol*. 1996;76:295-297.
69. Asero R, Tedeschi A. Usefulness of a short course of oral prednisone in antihistamine-resistant chronic urticaria:a retrospective analysis. *J Investig Allergol Clin Immunol*. 2010;20:386-390.
70. Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA(2)LEN/EDF/WAO guideline:management of urticaria. *Allergy*. 2009;64:1427-1443.
71. Rutkowski K, Grattan CEH. How to manage chronic urticaria 'beyond' guidelines:a practical algorithm. *Clin Exp Allergy*. 2017;47:710-718.
72. Magerl M, Philipp S, Manasterski M, et al. Successful treatment of delayed pressure urticaria with anti-TNF-alpha. *J Allergy Clin Immunol*. 2007;119:752-754.
73. O'Donnell BF, Barr RM, Black AK, et al. Intravenous immunoglobulin in autoimmune chronic urticaria. *Br J Dermatol*. 1998;138:101-106.
74. Dawn G, Urcelay M, Ah-Weng A, et al. Effect of high-dose intravenous immunoglobulin in delayed pressure urticaria. *Br J Dermatol*. 2003;149:836-840.
75. Pereira C, Tavares B, Carrapatoso I, et al. Low-dose intravenous gammaglobulin in the treatment of severe autoimmune urticaria. *Eur Ann Allergy Clin Immunol*. 2007;39:237-242.
76. Mitzel-Kaoukhov H, Staubach P, Muller-Brenne T. Effect of high-dose intravenous immunoglobulin treatment in therapy-resistant chronic spontaneous urticaria. *Ann Allergy Asthma Immunol*. 2010;104:253-258.
77. Bangsgaard N, Skov L, Zachariae C. Treatment of refractory chronic spontaneous urticaria with adalimumab. *Acta Derm Venereol*. 2017;97:524-525.
78. Sand FL, Thomsen SF. TNF-Alpha Inhibitors for Chronic Urticaria:Experience in 20 Patients. *J Allergy (Cairo)*. 2013;2013:130905.
79. Hannuksela M, Kokkonen EL. Ultraviolet light therapy in chronic urticaria. *Acta Derm Venereol*. 1985;65:449-450.
80. Borzova E, Rutherford A, Konstantinou GN, et al. Narrowband ultraviolet B phototherapy is beneficial in antihistamine-resistant symptomatic dermographism:a pilot study. *J Am Acad Dermatol*. 2008;59:752-757.
81. Engin B, Ozdemir M, Balevi A, Mevlitoglu I. Treatment of chronic urticaria with narrowband ultraviolet B phototherapy:a randomized controlled trial. *Acta Derm Venereol*. 2008;88:247-251.
82. Thormann J, Laurberg G, Zachariae H. Oral sodium cromoglycate in chronic urticaria. *Allergy*. 1980;35:139-141.
83. Laurberg G. Tranexamic acid (Cyklokapron) in chronic urticaria:a double-blind study. *Acta Derm Venereol*. 1977;57:369-370.
84. Lawlor F, Ormerod AD, Greaves MW. Calcium antagonist in the treatment of symptomatic dermographism. Low-dose and high-dose studies with nifedipine. *Dermatologica*. 1988;177:287-291.
85. Lawlor F, Black AK, Ward AM, et al. Delayed pressure urticaria, objective evaluation of a variable disease using a dermographometer and assessment of treatment using colchicine. *Br J Dermatol*. 1989;120:403-408.
86. Dover JS, Black AK, Ward AM, Greaves MW. Delayed pressure urticaria. Clinical features, laboratory investigations, and response to therapy of 44 patients. *J Am Acad Dermatol*. 1988;18:1289-1298.
87. Asero R, Tedeschi A, Cugno M. Heparin and tranexamic Acid therapy may be effective in treatment-resistant chronic urticaria with elevated d-dimer:a pilot study. *Int Arch Allergy Immunol*. 2010;152:384-389.
88. Novak Z, Yanez A, Kiss I, et al. Safety and tolerability of bilastine 10 mg administered for 12 weeks in children with allergic diseases. *Pediatr Allergy Immunol*. 2016;27:493-498.

89. Nayak AS, Berger WE, LaForce CF, et al. Randomized, placebo-controlled study of cetirizine and loratadine in children with seasonal allergic rhinitis. *Allergy Asthma Proc*. 2017;38:222-230.
90. Gupta S, Khalilieh S, Kantesaria B, Banfield C. Pharmacokinetics of desloratadine in children between 2 and 11 years of age. *Br J Clin Pharmacol*. 2007;63:534-540.
91. Gupta SK, Kantesaria B, Banfield C, Wang Z. Desloratadine dose selection in children aged 6 months to 2 years:comparison of population pharmacokinetics between children and adults. *Br J Clin Pharmacol*. 2007;64:174-184.
92. Meltzer EO, Scheinmann P, Rosado Pinto JE, et al. Safety and efficacy of oral fexofenadine in children with seasonal allergic rhinitis – a pooled analysis of three studies. *Pediatr Allergy Immunol*. 2004;15:253-260.
93. Pampura AN, Papadopoulos NG, Spicak V, Kurzawa R. Evidence for clinical safety, efficacy, and parent and physician perceptions of levocetirizine for the treatment of children with allergic disease. *Int Arch Allergy Immunol*. 2011;155:367-378.
94. Potter P, Mitha E, Barkai L, et al. Rupatadine is effective in the treatment of chronic spontaneous urticaria in children aged 2–11 years. *Pediatr Allergy Immunol*. 2016;27:55-61.
95. Weber-Schoendorfer C, Schaefer C. The safety of cetirizine during pregnancy. A prospective observational cohort study. *Reprod Toxicol*. 2008;26:19-23.
96. Schwarz EB Moretti ME, Nayak S, Koren G. Risk of hypospadias in offspring of women using loratadine during pregnancy:a systematic review and meta-analysis. *Drug Saf*. 2008;31:775-788.
97. Namazy J, Cabana MD, Scheuerle AE, et al. The Xolair Pregnancy Registry (EXPECT):the safety of omalizumab use during pregnancy. *J Allergy Clin Immunol*. 2015;135:407-412.
98. González-Medina M, Curto-Barredo L, Labrador-Horrillo M, Giménez-Arnau A. Omalizumab use during pregnancy for chronic spontaneous urticaria (CsU):report of two cases. *J Eur Acad Dermatol Venereol*. 2017;31:e245-e246.
99. Ghazanfar MN, Thomsen SF. Successful and safe treatment of chronic spontaneous urticaria with omalizumab in a woman during two consecutive pregnancies. *Case Rep Med*. 2015;2015:368053.

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