The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

Short running title:

International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for Urticaria

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Important: As this is an international guideline, no comment is given regarding the licensing of the drugs mentioned for the treatment of urticaria. It is in the duty of the treating physician to adhere to the relevant local regulations.

Notes on use/Disclaimer: This is an updated version of the international urticaria guideline. It is based on the update and revision of this guideline published in 2018: Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, Bernstein JA, Bindslev-Jensen C, Brzoza Z, Buense Bedrikow R, Canonica GW, Church MK, Craig T, Danilycheva IV, Dressler C, Ensina LF, Giménez-Arnau A, Godse K, Gonçalo M, Grattan C, Hebert J, Hide M, Kaplan A, Kapp A, Katelaris CH, Kocatürk E, Kulthanan K, Larenas-Linnemann D, Leslie TA, Magerl M, Mathelier-Fusade P, Meshkova RY, Metz M, Nast A, Nettis E, Oude-Elberink H, Rosumeck S, Saini SS, Sánchez-Borges M, Schmid-Grendelmeier P, Staubach P, Sussman G, Toubi E, Vena GA, Vestergaard C, Wedi B, Werner RN, Zhao Z, Maurer M; The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy 2018;73:1393-1414.

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for Urticaria was developed in accordance with the EuroGuiDerm Methods Manual v1.3, which can be found on the website of the European Dermatology Forum (EDF), subsection EuroGuiDerm/EDF Guidelines at https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html.

Abstract

This update and revision of the international guideline for urticaria was developed following the methods recommended by Cochrane and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group. It is a joint initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the Global Allergy and Asthma European Network (GA²LEN) and its Urticaria and Angioedema Centers of Reference and Excellence (UCAREs and ACAREs), the European Dermatology Forum (EDF; EuroGuiDerm), and the Asia Pacific Association of Allergy, Asthma and Clinical Immunology with the participation of 64 delegates of 50 national and international societies and from 31 countries. The consensus conference was held on 3 December 2020. This guideline was acknowledged and accepted by the European Union of Medical Specialists (UEMS).

Urticaria is a frequent, mast-cell-driven disease that presents with wheals, angioedema, or both. The lifetime prevalence for acute urticaria is approximately 20%. Chronic urticaria, i.e. chronic spontaneous urticaria and chronic inducible urticaria, is disabling, impairs quality of life, and affects performance at work and school. This updated version of the international guideline for urticaria covers the definition and classification of urticaria and outlines expert-guided and evidence-based diagnostic and therapeutic approaches for the different subtypes of urticaria.

Keywords: urticaria, angioedema, consensus, evidence-based, hives, wheal, itch, mast cell

Abbreviations

AAS	Angioedema activity score
ACARE	Angioedema Center of Reference and Excellence
ACE	Angiotensin-converting enzyme
AECT	Angioedema Control Test
AE-QoL	Angioedema Quality of Life Questionnaire
AGREE	Appraisal of Guidelines Research and Evaluation
AOSD	Adult-onset Still's disease
APAAACI	Asia Pacific Association of Allergy, Asthma and Clinical Immunology
ARIA	Allergic Rhinitis and Its Impact on Asthma
ASST	Autologous Serum Skin Test
BAT	Basophil activation test
BHRA	Basophil histamine release assay
CAPS	Cryopyrin-associated periodic symptoms
CIndU	Chronic inducible urticaria
CNS	Central nervous system
CSU	Chronic spontaneous urticaria
CU	Chronic urticaria
CU-Q2oL	Chronic urticaria Quality of Life Questionnaire
CYP	Cytochrome P
EAACI	European Academy of Allergology and Clinical Immunology
EDF	European Dermatology Forum
EtD	Evidence-to-Decision
FCAS	Familial Cold Autoinflammatory Syndrome
GA^{2}LEN	Global Asthma and Allergy European Network
GDT	Guideline Development Tool
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAE	Hereditary angioedema
HIDS	Hyper-IgD syndrome
IVIG (also IGIV)	Intravenous immunoglobulins
MWS	Muckle-Wells-Syndrome
NOMID	Neonatal Onset Multisystem Inflammatory Disease

NSAID	Non-steroidal anti-inflammatory drugs
PAF	Platelet activating factor
PROM	Patient-reported outcome measure
PET	Positron Emission Tomography
PICO	Technique used in Evidence-based Medicine, acronym stands for: Patient/Problem/Population, Intervention, Comparison/Control/Comparator, Outcome
REM	Rapid eye movement
sJIA	Systemic-onset juvenile idiopathic arthritis
TRAPS	Tumor necrosis factor receptor alpha-associated periodic syndrome
UAS	Urticaria activity score
UCARE	Urticaria Center of Reference and Excellence
UCT	Urticaria Control Test
UEMS	European Union of Medical Specialists
UV	Ultraviolet
WHO	World Health Organization

1. INTRODUCTION

This update and revision of the international guideline for urticaria is based on evidence and expert consensus and was developed following the methods recommended by Cochrane and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group. A structured consensus process was used to discuss and agree upon recommendations. The conference was held in a hybrid format on 3 December 2020, in Berlin, Germany and online.

The guideline is a joint initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the Global Allergy and Asthma European Network (GA²LEN) and its Urticaria and Angioedema Centers of Reference and Excellence (UCAREs and ACAREs), the European Dermatology Forum (EDF), and the Asia Pacific Association of Allergy, Asthma and Clinical Immunology. All of these organizations provided funding for the development of the guideline, which is an update and revision of the EAACI/GA²LEN/EDF/WAO guideline on urticaria published in 2018.[1-4] There was no funding from other sources.

The present update and revision of the guideline was undertaken by a panel of 64 urticaria experts from 31 countries, nominated as delegates by 50 participating national and/or international medical or scientific societies (Table 1). All of the societies involved endorse the guideline. The work of the expert panel was supported by a team of EuroGuiDerm methodologists led by Prof. Alexander Nast (Table 2) and included the contributions of the participants of the consensus conference.

Table 1. Members of the expert panel

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Table 2. Members of the EuroGuiDerm guideline methodology group

Title	First name	Last name	Country	Organization	Role
	Martin	Dittmann	Germany	Division of Evidence-Based Medicine (dEBM), Charité – Universitätsmedizin Berlin	Information specialist, team support
Dr.	Corinna	Dressler	Germany	Division of Evidence-Based Medicine (dEBM), Charité – Universitätsmedizin Berlin	Methodologist
	Matthew	Gaskins	Germany	Division of Evidence-Based Medicine (dEBM), Charité – Universitätsmedizin Berlin	Methodologist
Prof. Dr.	Alexander	Nast	Germany	Division of Evidence-Based Medicine (dEBM), Charité – Universitätsmedizin Berlin	Methodologist, conference facilitator

The aim of the guideline is to provide a definition and classification of urticaria, thereby facilitating the interpretation of data from different centers and areas of the world regarding underlying causes, eliciting factors, comorbidities, burden to patients and society, and therapeutic responsiveness of subtypes of urticaria. Furthermore, the guideline provides recommendations for diagnostic and therapeutic approaches in common subtypes of urticaria. This is an international guideline and takes into consideration the global diversity of patients, physicians, medical systems and access to diagnosis and treatment.

2. METHODS

The detailed methods used to develop this guideline are published as a separate Methods Report, which is available on the EDF website alongside a separate Evidence Report including all evidence-to-decision frameworks (https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html).

The guideline takes into account the Appraisal of Guidelines Research and Evaluation (AGREE II) Instrument[5] and the methods suggested by the GRADE working group. The literature review was conducted using the methods given in the Cochrane Handbook for Systematic Reviews of Interventions.[6]

In summary, experts from 50 societies were nominated to be involved in the development of this update and revision of the guideline. All members of the expert panel received an invitation to submit a declaration of their conflicts of interest (COIs) online and to self-declare their personal-financial interests (P-F), non-personal financial interests (NP-F), and personal non-financial interests (P-NF). An overview of the declarations of P-F conflicts of interests is given in the Methods Report. Overall, 40 members of the expert panel (62.5%) declared that they had no P-F COIs.

For the 2021 update of the guideline, the same key questions were used as those developed for the version of the guideline published in 2018. Details on the processes used to develop these questions are available in the Methods Report of the latter.[7] The key questions were translated into the PICO format, which specifies the intervention, comparison and outcome used to assess efficacy and safety, and are included in the header of each evidence-to-decision framework. Systematic searches for randomized controlled trials and clinical controlled trials were undertaken in three databases on 15 May 2020.

The search identified a total of 2053 records. Two independent reviewers evaluated the literature and extracted eligible data. The removal of duplicates and title/abstract screening left 144

records to be assessed as full texts for eligibility, of which 123 were excluded. A total of 21 records were determined to fulfil the inclusion criteria. A graphical breakdown of this process and a list of excluded full-text publications with reasons for exclusion can be found in the separate Methods Report.

Wherever possible, we calculated effect measures with confidence intervals and performed meta-analyses using Review Manager.[8] We assessed the quality of the evidence following the GRADE approach using GRADEpro Guideline Development Tool (GDT).[9,10] Five criteria (risk of bias, inconsistency, indirectness, imprecision and publication bias) were evaluated for each outcome resulting in an overall assessment of quality of evidence (Table 3). Effect measures such as risk ratios express the size of an effect, and the quality rating expresses how much confidence one can have in a result.

Table 3. Summary of the GRADE approach to assessing the quality of evidence by outcome in randomized controlled trials[11]

Initial rating of 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.

Subsequently, evidence-to-decisions frameworks were created to help the expert panel make judgements for specific comparisons about the size of the desirable and undesirable effects, as well as the balance between these, and to provide an overview of the quality of the evidence. The evidence assessment yielded 14 new or updated GRADE evidence profiles and 14 new or updated evidence-to-decision frameworks. A summary of the evidence is given in the separate

Evidence Report. Recommendations for each of the evidence-based key questions were subsequently drafted using standardized wording (Table 4).

Table 4. Standardized wording and symbols for guideline recommendations

Strength of recommendation	Wording	Symbols	Implications
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 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.
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 (for example, 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.

Before the consensus conference, two rounds of pre-voting were held via an online survey to familiarize the expert panel with all of the draft recommendations and evidence-to-decision frameworks, gather their feedback on these, and subsequently use this feedback to modify the recommendations or to draft alternatives to them to be presented and voted upon during the consensus conference. All members of the expert panel were eligible for pre-voting (regardless of whether they had P-F conflicts of interests). Of 61 members of the expert panel, 50 completed the first survey (response rate 81.9%), which focused on the diagnosis and classification section of the guideline, and 60 completed the second survey (response rate 98.4%), which focused on the management section of the guideline. The results were either fed back to the expert panel

or integrated into the evidence-to-decision frameworks. All evidence-to-decision frameworks and draft recommendations were made available in advance to the participants of the consensus conference.

The consensus conference took place on 3 December 2020 and was held in a hybrid format. Participants consisted of the members of the expert panel and a broader group of up to 100 professionals comprising physicians regularly involved in treating patients with urticaria, basic or clinical researchers in the field, and representatives of patient organizations and advocacy groups. Voting took place online using the Slido© polling platform. To be able to vote, participants were required to have submitted a conflict of interest declaration. Everyone except for those employed at a pharmaceutical company was eligible to vote and received a code to access the live polls. During the conference, the nominal group technique was used to discuss, modify and reach agreement on the different recommendations[12]: Each draft recommendation was presented alongside the relevant evidence or justification; this was followed by open discussion, preliminary voting or collection of suggestions for alternative wording, and then the final vote. Strong consensus was defined as 90% agreement or higher, and consensus as 70-89% agreement. All recommendations were voted on by at least 89 participants and were passed with at least 75% agreement.

After the conference, the text of the previous version of the guideline published in 2018 was amended by the guideline coordinators and the methodologist team in line with the results of the voting and the points discussed during the conference and the pre-conference rounds of online voting. The draft was subsequently reviewed internally by the expert panel and externally by the participating national and international societies.

In the guideline itself, the strength of the consensus reached for each recommendation is reported as shown in Table 5.

Table 5. Definitions of strength of consensus

Strong consensus	Agreement of ≥90% participants
Consensus	Agreement of 70-89% participants
Agreement of the majority	Agreement of 51-69% participants

Each recommendation in the guideline is formatted as shown in Boxes 1-3. At the top of each box, the question of interest is given (e.g., "Should we … in chronic urticaria?"). In the row

below the question of interest, the recommendation is spelled out in full using the standardized wording and symbols shown in Table 4. In Box 1, for example, we can see that a strong recommendation is being made (i.e., "We recommend…" and "↑↑" in dark green). Additionally, we can see, based on the information given on the right-hand side of this same row, that the eligible participants in the consensus conference agreed upon this recommendation and its wording with strong consensus (≥90% agreement) and that the recommendation is based on expert consensus. If the recommendation is based, additionally, on evidence from a systematic review of the literature, the phrase used here will read "Evidence- and consensus-based (see Evidence Report)" instead of "Expert consensus".

If there are multiple recommendations that address the same question of interest and each of these recommendations was voted upon separately, these can be grouped together as shown in Box 2. In this case, the strength of consensus and the evidence base are given for each recommendation separately.

In Box 3, we also see two recommendations instead of one. However, in this case, because these were voted on jointly in the consensus conference, the information on the strength of consensus and the evidence base are shown only once and apply to both recommendations.

Box 1. Format for individual guideline recommendations, including strength of consensus and evidence base

Should we … in chronic urticaria?		
We **recommend** that …	↑↑	Strong consensus[1] Expert consensus
[1] ≥90% agreement		

Box 2. Format for multiple guideline recommendations voted upon separately, including strength of consensus and evidence base for each

Should we … in chronic urticaria?		
We **recommend** that …	↑↑	Strong consensus[1] Expert consensus
[1] ≥90% agreement		
We **suggest** that …	↑	Strong consensus[1] Expert consensus
[1] ≥90% agreement		

Box 3. Format for multiple guideline recommendations voted on jointly, including strength of consensus and evidence base

Should we … in chronic urticaria?		
We **recommend** that … We **recommend** using …	↑↑	Strong consensus[1] Expert consensus
[1] ≥90% agreement		

3. DEFINITION

3.1 Definition

Urticaria is a condition characterized by the development of wheals (hives), angioedema, or both. Urticaria needs to be differentiated from other medical conditions where wheals, angioedema, or both can occur as part of the spectrum of clinical features, e.g. anaphylaxis, autoinflammatory syndromes, urticarial vasculitis, or bradykinin-mediated angioedema including hereditary angioedema (HAE).

Definition
Urticaria is a condition characterized by the development of wheals (hives), angioedema or both.

A) A wheal has three typical features:
   1. a central swelling of variable size, almost invariably surrounded by reflex erythema,
   2. an itching or sometimes burning sensation,
   3. a fleeting nature, with the skin returning to its normal appearance, usually within 30 minutes to 24 h.

B) Angioedema is characterized by:
   1. a sudden, pronounced erythematous or skin colored swelling of the lower dermis and subcutis or mucous membranes,
   2. sometimes pain, rather than itch,
   3. a resolution slower than that of wheals (can take up to 72 hours).

3.2 Classification of urticaria on the basis of its duration and the relevance of eliciting factors

The spectrum of clinical manifestations of different urticaria types and subtypes is very wide. Additionally, two or more different subtypes of urticaria can coexist in any given patient.

Urticaria is classified based on its duration, as acute or chronic, and the role of definite triggers, as inducible or spontaneous. Acute urticaria is defined as the occurrence of wheals, angioedema or both for six weeks or less. Chronic urticaria is defined as the occurrence of wheals, angioedema, or both for more than six weeks. Chronic urticaria can come with daily or almost daily signs and symptoms or an intermittent / recurrent course.

Inducible urticaria is characterized by definite and subtype-specific triggers of the development of wheals, angioedema, or both. These triggers are definite because wheals, angioedema or both always and never occur when the trigger is present and absent, respectively. These triggers are specific because each subtype of inducible urticaria has its relevant trigger, for example cold in cold urticaria, and this trigger is not relevant in other forms of inducible urticaria. Rare subtypes of inducible urticaria exist in which the combined presence of two or more definite and specific triggers is required for the induction of wheals, angioedema or both, for example cholinergic cold urticaria.

Some patients with spontaneous urticaria experience trigger-induced wheals, angioedema, or both. These triggers are not definite, as their presence does not always induce signs and symptoms and because wheals, angioedema or both also occur without them, i.e. spontaneously. Some patients can present with more than one subtype of urticaria, which can also respond independently to treatment.

How should urticaria be classified?		
We **recommend** that urticaria is classified based on its duration as acute (< =6 weeks) or chronic (> 6 weeks).	↑↑	Strong consensus[1] Expert consensus
[1] ≥90% agreement		
We **recommend** that urticaria is classified as spontaneous (no definite eliciting factor involved) or inducible (specific definite factor involved).	↑↑	Strong consensus[1] Expert consensus
[1] ≥90% agreement		

Table 6 shows the classification of chronic urticaria (CU) subtypes for clinical use. This classification has been maintained from the previous version of the guideline by strong consensus (≥90%).

Should we maintain the current guideline classification of chronic urticaria?		
We **recommend** that the current guideline classification of chronic urticaria should be maintained.	↑↑	Strong consensus[1] Expert consensus
[1] ≥90% agreement		

Table 6. Recommended classification of chronic urticaria

Chronic Urticaria Subtypes	
Chronic Spontaneous Urticaria (CSU)	**Inducible Urticaria**
Spontaneous appearance of wheals, angi-oedema or both for > 6 weeks due to known[1] or unknown causes	Symptomatic dermographism[2] Cold urticaria[3] Delayed pressure urticaria[4] Solar urticaria Heat urticaria[5] Vibratory angioedema[6] Cholinergic urticaria Contact urticaria Aquagenic urticaria[6]
[1] For example, type I autoimmunity (autoallergy) and type IIb autoimmunity, with mast cell-activating autoantibodies; [2] Formerly called *urticaria factitia* or dermographic urticaria; [3] Also called cold contact urticaria; [4] Also called pressure urticaria; [5] Also called heat contact urticaria; [6] Also called Vibratory angioedema/urticaria. Chronic urticaria (CU) is classified as spontaneous (CSU) and inducible (CIndU). CSU comes as CSU with known cause and CSU with unknown cause. CIndU is further subclassified as symptomatic dermographism, cold urticaria, delayed pressure urticaria, solar urticaria, heat urticaria, and vibratory angioedema (collectively referred to as chronic physical urticaria), as well as cholinergic urticaria, contact urticaria, and aquagenic urticaria. CU patients can have more than one form of CU including more than one form of CIndU and they often do. Table is based on expert consensus and achieved ≥90% agreement in the consensus conference.	

Urticarial vasculitis, maculo-papular cutaneous mastocytosis (formerly called urticaria pigmentosa) and indolent systemic mastocytosis with involvement of the skin, mast cell activation syndrome (MCAS), auto-inflammatory syndromes (e.g. cryopyrin-associated periodic syndromes or Schnitzler's syndrome), non-mast cell mediator-mediated angioedema (e.g. bradykinin-mediated angioedema), and other diseases and syndromes that can manifest with wheals and/or angioedema are not considered to be types of urticaria, due to their distinctly different pathophysiologic mechanisms and/or clinical presentation (Table 7).

Table 7. Diseases related to urticaria for historical reasons, and syndromes that present with hives and/or angioedema

- Maculopapular cutaneous mastocytosis (urticaria pigmentosa) and indolent systemic mastocytosis with involvement of the skin
- Mast cell activation syndrome (MCAS)
- Urticarial vasculitis
- Bradykinin-mediated angioedema (e.g. HAE)
- Exercise-induced anaphylaxis
- Cryopyrin-associated periodic syndromes (CAPS; urticarial rash, recurrent fever attacks, arthralgia or arthritis, eye inflammation, fatigue and headaches), i.e. Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS) or Neonatal Onset Multisystem Inflammatory Disease (NOMID).
- Schnitzler's syndrome (recurrent urticarial rash and monoclonal gammopathy, recurrent fever attacks, bone and muscle pain, arthralgia or arthritis and lymphadenopathy)
- Gleich's syndrome (episodic angioedema with eosinophilia)
- Well's syndrome (granulomatous dermatitis with eosinophilia/eosinophilic cellulitis)
- Bullous pemphigoid (prebullous stage)
- Adult-onset Still's disease (AOSD)

These diseases and syndromes are related to urticaria 1) because they can present with wheals, angioedema, or both and/or 2) because of historical reasons. They are differential diagnoses of urticaria.

3.3 Pathophysiological aspects

Urticaria is a mast cell-driven disease.[13] Histamine and other mediators, such as platelet-activating factor (PAF) and cytokines released from activated skin mast cells, result in sensory nerve activation, vasodilatation and plasma extravasation as well as cell recruitment to urticarial lesions. The mast cell-activating signals in urticaria are heterogeneous, diverse, and include autoantibodies. Histologically, wheals are characterized by edema of the upper and mid dermis, with dilatation and augmented permeability of the postcapillary venules, as well as lymphatic vessels of the upper dermis leading to leakage of serum into the tissue. In angioedema, similar changes occur primarily in the lower dermis and the subcutis. Skin affected by wheals shows a

mixed inflammatory perivascular infiltrate of variable intensity, consisting of T cells, eosinophils, basophils, and other cells. Vessel-wall necrosis, a hallmark of urticarial vasculitis, does not occur in urticaria.[14-18] The nonlesional skin of chronic spontaneous urticaria (CSU) patients shows upregulation of adhesion molecules, infiltrating eosinophils, altered cytokine expression[19] and sometimes a mild to moderate increase of mast cell numbers.[13] These findings underline the complex nature of the pathogenesis of urticaria, which has many features in addition to the release of histamine from dermal mast cells.[20-22] Some of these features of urticaria are also seen in a wide variety of inflammatory conditions and are thus not specific or of diagnostic value. A search for more specific histological bio-markers for different subtypes of urticaria and for distinguishing urticaria from other conditions is desirable.[23]

3.4 Burden of disease

The burden of CU for patients, their family and friends, the health care system and society is substantial.[24] The use of patient-reported outcome measures such as the urticaria activity score (UAS), the angioedema activity score (AAS), the CU quality of life questionnaire (CU-Q2oL), the angioedema quality of life questionnaire (AE-QoL), the urticaria control test (UCT), and the angioedema control test (AECT) in studies and clinical practice has helped to better define the effects and impact of CU on patients.[25] The available data indicate that urticaria markedly affects both objective functioning and subjective well-being.[26-28] Previously, O'Donnell et al. showed that health status scores in CSU patients are comparable to those reported by patients with coronary artery disease.[29] Furthermore, both health status and subjective satisfaction in patients with CSU are lower than in healthy subjects and in patients with respiratory allergy.[30] CU also comes with considerable costs for patients and society.[31-33]

4. Diagnosis of Urticaria

Detailed history taking is essential in urticaria; it is the first step in the diagnostic workup of all urticaria patients. The second step is the physical examination of the patient. As wheals and angioedema are transient and may not be present at the time of physical examination, it is important to review patients' documentation of signs and symptoms (including pictures of wheals and/or angioedema). The third step, in chronic urticaria, is a basic diagnostic work-up, with limited tests (see Table 8; recommended routine diagnostic tests). Further individually selected diagnostic tests may be useful, based on the outcome of the first three steps and depending on the urticaria type and subtype (Table 8; extended diagnostic program). The aims of all diagnostic tests performed should be clear to the physician and patient.

Table 8. Recommended diagnostic tests in frequent urticaria subtypes

Types	Subtypes	Routine diagnostic tests (recommended)	Extended diagnostic programme[1] (based on history) – For identification of underlying causes or eliciting factors and for ruling out possible differential diagnoses if indicated
Spontaneous urticaria	Acute spontaneous urticaria	None	None[2]
	CSU	Differential blood count. ESR and/ or CRP IgG anti-TPO and total IgE[5]	Avoidance of suspected triggers (e.g. drugs); Diagnostic tests for (in no preferred order): (i) infectious diseases (e.g. *Helicobacter pylori*); (ii) functional autoantibodies (e.g. basophil test); (iii) thyroid gland disorders (thyroid hormones and autoantibodies); (iv) allergy (skin tests and/or allergen avoidance test, e.g. avoidance diet); (v) concomitant CIndU, see below [34](vi) severe systemic diseases (e.g. tryptase); (vii) other (e.g. lesional skin biopsy)
Inducible urticaria	Cold urticaria	Cold provocation and threshold test[3,4]	Differential blood count and ESR or CRP, rule out other diseases, especially infections[35]
	Delayed pressure urticaria	Pressure test and threshold test[3,4]	None
	Heat urticaria	Heat provocation and threshold test[3,4]	None
	Solar urticaria	UV and visible light of different wave lengths and threshold test[3]	Rule out other light-induced dermatoses
	Symptomatic dermographism	Elicit dermographism and threshold test[3,4]	Differential blood count, ESR or CRP
	Vibratory angioedema	Test with vibration e.g. Vortex or mixer[4]	None
	Aquagenic urticaria	Provocation testing[4]	None
	Cholinergic urticaria	Provocation and threshold testing[4]	None
	Contact urticaria	Provocation testing[4]	None

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.
[1] Depending on suspected cause.
[2] Unless strongly suggested by patient history, e.g. allergy.
[3] All tests are done with different levels of the potential trigger to determine the threshold.
[4] For details on provocation and threshold testing see [34]
[5] For patients in specialist care

4.1 Diagnostic work up in acute urticaria

Acute urticaria, because it is self-limiting, usually does not require a diagnostic workup. The only exception is the suspicion of acute urticaria due to a type I food allergy in sensitized patients or drug hypersensitivity, especially for non-steroidal anti-inflammatory drugs (NSAIDs). In this case, allergy tests and patient education may be useful to allow patients to avoid re-exposure to relevant causative factors.

Should routine diagnostic measures be performed in acute urticaria?		
We **recommend against** any routine diagnostic measures in acute spontaneous urticaria.	↓↓	Strong consensus[1] Expert consensus
[1] ≥90% agreement		

4.2 Diagnostic work up in CSU

In CSU, the diagnostic work up has seven major aims. They are to confirm the diagnosis and exclude differential diagnoses; to look for the underlying causes; to identify relevant conditions that modify disease activity; to check for comorbidities; to identify the consequences of CSU; to assess predictors of the course of disease and response to treatment; and to monitor disease activity, impact and control (Table 9).[36]

Table 9. The aims of the diagnostic work up in patients with CSU[36]

What to do in every CSU patient			
History	Physical examination[1]	Basic tests[2]	UCT
Confirm	Rule out differential diagnoses		
Cause	Look for indicators of CSU^{aiTI}, CSU^{aiTIIb}		
Cofactors	Identify potential triggers, aggravators		
Comorbidities	e.g. check for CIndU, autoimmunity, mental health		
Consequences	e.g. identify problems with sleep, distress, sexual health, work, social performance		
Components	Assess potential biomarkers or predictors of treatment response		
Course	Monitor CSU activity, impact and control		

CSU = chronic spontaneous urticaria; CSU^{aiTI} = Type I autoimmune (autoallergic) CSU; CSU^{aiTIIb} = Type IIb autoimmune CSU; UCT = urticaria control test
[1] Including review of patient photo documentation
[2] Differential blood count, CRP/Erythrocyte sedimentation rate; IgG-anti-TPO, total IgE for patients in specialist care

In all CSU patients, the diagnostic workup includes a thorough history, physical examination (including review of pictures of wheals and/or angioedema), basic tests, and the assessment of disease activity, impact and control. The basic tests include a differential blood count and CRP

and/or ESR, in all patients, and total IgE and IG-anti-TPO, in patients in specialist care. Based on the results obtained by these measures, further diagnostic testing may be performed as indicated.

4.2.1 Confirmation of CSU and exclusion of differential diagnoses

Wheals or angioedema also occur in patients with diseases other than CSU. In patients who exclusively develop wheals (but not angioedema), urticarial vasculitis and autoinflammatory disorders such as Schnitzler syndrome or cryopyrin-associated periodic syndromes (CAPS) need to be ruled out. On the other hand, in patients who suffer exclusively from recurrent angioedema (but not from wheals), bradykinin-mediated angioedema like angiotensin-converting-enzyme (ACE)-inhibitor induced angioedema and HAE should be considered as differential diagnoses (Figure 1). The assessment of patients for differential diagnoses of CSU is guided by the history (Figure 1) and supported by basic tests, e.g. CRP and/or ESR, differential blood count. Further testing should be performed only as indicated by the results of the history, physical examination, and basic testing.

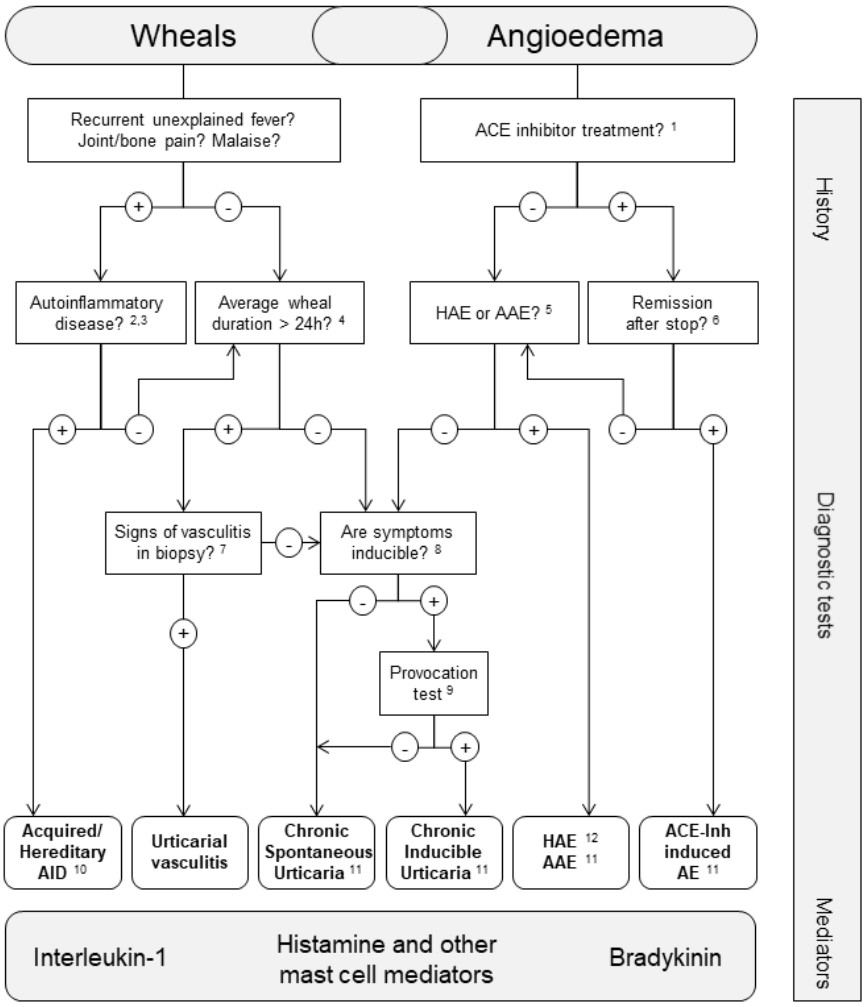


Figure 1. Diagnostic algorithm for patients presenting with wheals, angioedema, or both

AAE: Acquired angioedema due to C1-inhibitor deficiency; ACE-Inh: angiotensin converting enzyme inhibitor; AE: angioedema; AID: Auto-inflammatory disease; HAE: Hereditary angioedema

Figure 1 legend:

1 Apart from ACE inhibitors, angiotensin II type 1 receptor blockers (sartans), dipeptidyl peptidase IV inhibitors (gliptins) and neprilysin inhibitors have been described to induce angioedema but much less frequently

2 Patients should be asked for a detailed family history and age of disease onset

3 Test for elevated inflammation markers (C-reactive protein, erythrocyte sedimentation rate), test for paraproteinemia in adults, look for signs of neutrophil-rich infiltrates in skin biopsy; perform gene mutation analysis for hereditary periodic fever syndromes (e.g. Cryopyrin-associated periodic syndrome), if strongly suspected.

4 Patients should be asked: "For how long does each individual wheal last?"

5 Test for Complement C4, C1-INH levels and function; in addition test for C1q and C1-INH antibodies, if AAE is suspected; do gene mutation analysis, if former tests are unremarkable but patient's history suggests hereditary angioedema.

6 Remission should occur within a few days, in rare cases up to 6 months of ACE-inhibitor discontinuation.

7 Does the biopsy of lesional skin show damage of the small vessels in the papillary and reticular dermis and/or fibrinoid deposits in perivascular and interstitial locations suggestive of urticarial vasculitis?

8 Patients should be asked: "Can you make your wheals appear? Can you bring out your wheals?"

9 In patients with a history suggestive of inducible urticaria standardized provocation testing according to international consensus recommendations [34] should be performed.

10 Acquired autoinflammatory syndromes include Schnitzler's syndrome as well as systemic-onset juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD); hereditary autoinflammatory syndromes include Cryopyrin-associated periodic syndromes (CAPS) such as familial cold auto-inflammatory syndromes (FCAS), Muckle-Wells syndrome (MWS) and neonatal onset multisystem inflammatory disease (NOMID), more rarely hyper-IgD syndrome (HIDS) and tumor necrosis factor receptor alpha-associated periodic syndrome (TRAPS).

11 In some rare cases recurrent angioedema is neither mast cell mediator-mediated nor bradykinin-mediated, and the underlying pathomechanisms remain unknown. These rare cases are referred to as "idiopathic angioedema" by some authors.

12 Several subtypes HAE are known: HAE-1: Hereditary angioedema due to C1-Inhibitor deficiency; HAE-2: Hereditary angioedema due to C1-Inhibitor dysfunction; HAE nC1-INH: Hereditary angioedema with normal C1-Inhibitor levels, either due to a mutation in FXII (factor 12), ANGPT1 (angiopoietin-1), PLG (plasminogen), KNG1 (kininogen), MYOF (myoferlin), and HS3ST6 (heparan sulfate-glucosamine 3-O-sulfotransferase 6) or unknown.

Should differential diagnoses be considered in patients with chronic spontaneous urticaria?		
We **recommend** that differential diagnoses be considered in all patients with signs or symptoms suggestive of chronic urticaria based on the guideline algorithm.	↑↑	Strong consensus[1] Expert consensus
[1] 100% agreement		

What routine diagnostic measures should be performed in chronic spontaneous urticaria?		
We **recommend** limited investigations. Basic tests include differential blood count, CRP and/or ESR, and in specialized care total IgE and IgG anti-TPO, and more biomarkers as appropriate. We **recommend** performing further diagnostic measures based on the patient history and examination, especially in patients with long standing and/or uncontrolled disease.	↑↑	Consensus[1] Expert consensus
[1] >75% agreement		

Should routine diagnostic measures be performed in inducible urticaria?		
We **recommend** using provocation testing to diagnose chronic inducible urticaria. We **recommend** using provocation threshold measurements and the UCT to measure disease activity and control in patients with chronic inducible urticaria, respectively.	↑↑	Strong consensus[1] Expert consensus
[1] ≥90% agreement		

4.2.2 Identification of underlying causes

Although the pathogenesis of CSU is not yet fully understood, it is well established that its signs and symptoms are due to the activation of skin mast cells and the subsequent release and effects of their mediators.[13] Based on recent evidence, it is known that the causes of CSU include autoimmunity Type I (CSU^{aiTI}, or "autoallergic CSU"; with IgE autoantibodies to self-antigens) and autoimmunity Type IIb (CSU^{aiTIIb}; with mast cell-directed activating autoantibodies). In CSU due to unknown cause (CSU^{uc}), as of yet unknown mechanisms are relevant for the degranulation of skin MC. The history and physical examination can provide clues on underlying causes. The results of the basic tests performed in CSU can point to CSU^{aiTI} vs CSU^{aiTIIb}, with CRP more often elevated and eosinophil and basophil levels more often reduced in CSU^{aiTIIb}. Testing for IgG-anti-TPO and total IgE, basic tests that should be performed in CSU patients in specialist care, can help to bring more clarity. CSU^{aiTIIb} patients are more likely to have low or very low total IgE and elevated levels of IgG-anti-TPO IgG, and a high ratio of

IgG-anti-TPO and low total IgE is currently the best surrogate marker for CSU^{aiTIIb}. More advanced tests, such as basophil activation testing for CSU^{aiTIIb} can bring more clarity, and should be guided by and based on the history, physical examination and results of basic testing. Other underlying causes include active thyroid disease, infections, inflammatory processes, food and drugs but these can be both cause as well as only aggravating factor and are covered below. Intensive and costly general screening programs for causes of urticaria are strongly advised against.

Importantly, there may be considerable variations in the frequency of underlying causes in different parts of the world, and regional differences are not well researched and understood.

4.2.3 Identification of relevant conditions that modify disease activity

Identifying relevant conditions that modify CSU disease activity and factors that exacerbate CSU, such as drugs, food, stress and infections, can help physicians and patients understand and sometimes change the course of CSU.

Drugs can trigger CSU exacerbation. NSAIDs are the most common drugs to do so, in up to one of four patients with the exception of paracetamol and/or COX-2 inhibitors as safer options in patients with CSU. Physicians should therefore ask patients about the intake of NSAIDs, including on demand use, and advise them that avoiding NSAIDs can prevent exacerbation. Provocation testing is usually not useful.

Food can trigger CSU exacerbation, and physicians should ask patients about this. Based on their answer, pseudoallergen- and histamine-low diets may be considered as an additional, individual diagnostic measure. Diagnostic diets should be maintained only for a limited time to avoid side-effects and safety risks; three to four weeks are usually recommended. Importantly, diagnostic diets should not delay effective treatment.[37]

Stress can exacerbate CSU, and up to one third of CSU patients see stress as an aggravating factor of their disease. Physicians should ask patients about the impact of stress on their disease and make them aware that stress reduction can be helpful.

4.2.4 Identification of comorbidities and consequences of CSU

In CSU, the most common comorbidities are CIndUs, autoimmune diseases and allergies. Mental disorders, i.e. depression and anxiety, sexual dysfunction and sleep disturbance are common

consequences. Findings from the patient's medical history, physical examination or basic testing that point to a comorbidity or consequence of CSU should prompt further investigations, for example screening for specific diseases by questionnaires, provocation tests, further laboratory tests or referral to a specialist.

4.2.5 Identification of predictors of the course of disease and response to treatment

In CSU, disease duration, disease activity and response to treatment are linked to clinical characteristics and laboratory markers. While none of these are definite predictors, they can help physicians to counsel their patients on the severity and expected duration of their disease and on what to expect from treatment. Comorbid CIndU, high disease activity, and elevated CRP, for example, point to long duration of CSU and poor response to antihistamine treatment.[24,38,39]

4.2.6 Assessment of disease activity, impact and control

Patients should be assessed for disease activity, impact and control at the first and every follow up visit. Validated patient-reported outcome measures (PROMs) such as the UAS (and the UAS7 calculated from it), AAS, CU-Q2oL, AE-QoL, UCT and AECT should be used for this purpose.[40,41] PROMs are available in a wide range of languages.

In CSU patients who develop wheals, disease activity should be assessed both in clinical care and trials with the UAS7 (Table 10), a unified and simple scoring system that was proposed in the last version of the guideline and has been validated.[42,43] The UAS7 is based on the assessment of key urticaria signs and symptoms (wheals and pruritus), which are documented by the patient, making this score especially valuable. The use of the UAS7 facilitates comparison of study results from different centers. As urticaria activity frequently changes, the overall disease activity is best measured by advising patients to document 24h self-evaluation scores once daily for several days. The UAS7, i.e. the sum score of 7 consecutive days, should be used in routine clinical practice to determine disease activity and response to treatment of patients with CSU. For CSU patients who develop angioedema, with or without wheals, the Angioedema Activity Score (AAS) should be used to assess disease activity (Table 10).[44] CSU patients who experience wheals and angioedema should use the UAS7 and the AAS in combination.

Table 10. The urticaria activity score (UAS) and Angioedema Activity Score (AAS) for assessing disease activity in CSU

Urticaria Activity Score (UAS)		
Score	**Wheals**	**Pruritus**
0	None	None
1	Mild (<20 wheals/24 h)	Mild (present but not annoying or troublesome)
2	Moderate (20–50 wheals/24 h)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (>50 wheals/24 h or large confluent areas of wheals)	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)
Angioedema Activity Score (AAS)		
Score	**Dimension**	**Answer options**
–	Have you had a swelling episode in the last 24 hours?	no, yes
0–3	At what time(s) of day was this swelling episode(s) present? (please select all applicable times)	midnight–8 a.m., 8 a.m.–4 p.m., 4 p.m.–midnight
0–3	How severe is / was the physical discomfort caused by this swelling episode(s) (e.g., pain, burning, itching?)	no discomfort, slight discomfort, moderate discomfort, severe discomfort
0–3	Are / were you able to perform your daily activities during this swelling episode(s)?	no restriction, slight restriction, severe restriction, no activities possible
0–3	Do / did you feel your appearance is / was adversely affected by this swelling episode(s)?	no, slightly, moderately, severely
0–3	How would you rate the overall severity of this swelling episode?	negligible, mild, moderate, severe

For the UAS7 the sum of score 0-6 for each day is summarized over one week (maximum 42). For the AAS, scores are summed up to an AAS day sum score (0-15), 7 AAS day sum scores to an AAS week sum score (AAS7, 0-105), and 4 ASS week sum scores may be summed up to an AAS 4-week sum score (AAS28, 0-420). Copyright for UAS: GA²LEN; copyright for AAS (UK version): MOXIE GmbH (www.moxie-gmbh.de)

In addition to disease activity, it is important to assess the impact of disease on quality of life as well as disease control both in clinical practice and trials. The CU-Q2oL should be used to determine QoL impairment in CSU patients with wheals. For CSU patients with angioedema, with or without wheals, the AE-QoL should be used. In CSU patients with wheals and angioedema, the CU-Q2oL and the AE-QoL should be used.

It is also important to assess disease control in patients with CSU. The Urticaria Control Test (UCT) should be used to do this in CSU patients who develop wheals, with or without angioedema (Figure 2A). For CSU patients who develop angioedema, with or without wheals, the Angioedema Control Test (AECT) should be used (Figure 2B). In CSU patients who develop wheals and angioedema, both the UCT and the AECT should be used. The UCT was developed and validated to determine the level of disease control in all forms of CU (CSU and CIndU).[45,46] The UCT is a simple four-item tool with a clearly defined cut off for patients with "well-controlled" vs. "poorly controlled" disease, and it is thus suited for the management of patients in routine clinical practice. The cut-off value for well-controlled disease is 12 out of 16 possible points. The AECT quantifies disease control in CSU patients with angioedema and patients with other forms of recurrent angioedema.[40] Like the UCT, the AECT is a retrospective PROM. Two versions exist, one with a 4-week recall period and one with a three-month recall period. The AECT consists, like the UCT, of only four questions. Its cut off for well controlled disease is 10 points. Both the UCT and the AECT are easy to administer, complete, and score, and can help to guide treatment decisions.

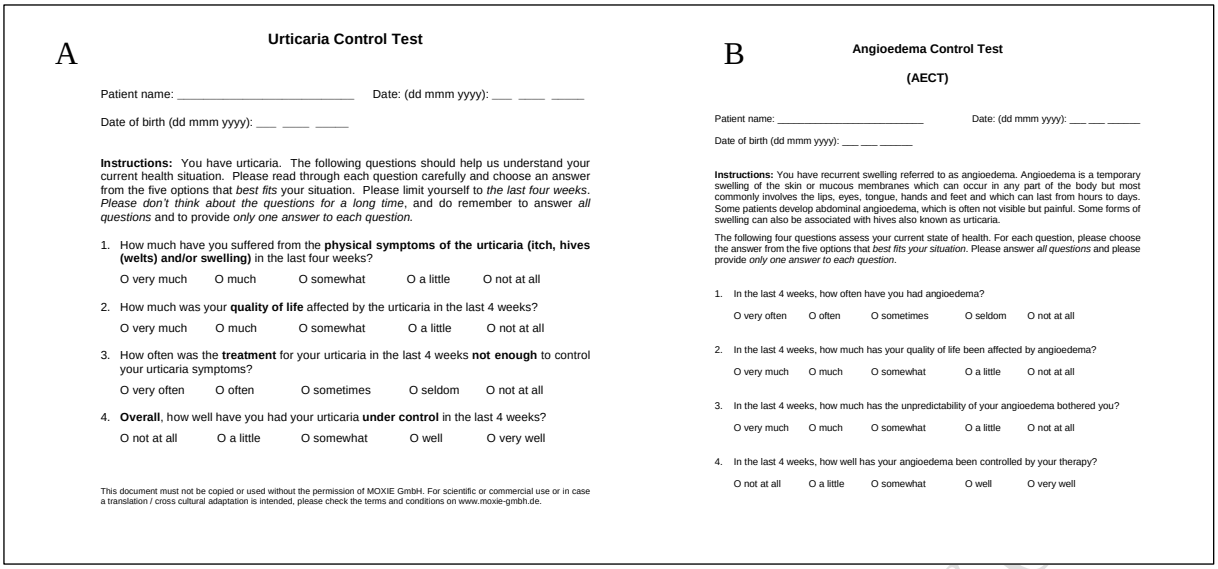
Should patients with chronic urticaria be assessed for disease activity, impact, and control?		
We **recommend** that patients with CU be assessed for disease activity, impact, and control at every visit.	↑↑	Strong consensus[1] Expert consensus
[1] ≥90% agreement		

Which instruments should be used to assess and monitor disease activity in chronic spontaneous urticaria patients?

We **recommend** the use of the urticaria activity score, UAS7, and of the angioedema activity score, AAS, for assessing disease activity in patients with chronic spontaneous urticaria.	↑↑	Strong consensus[1] Expert consensus
[1] ≥90% agreement		

Which instruments should be used to assess and monitor quality of life impairment in chronic spontaneous urticaria patients?		
We **recommend** the use of the chronic urticaria quality of life questionnaire, CU-Q2oL, and the angioedema quality of life questionnaire, AE-QoL, for assessing quality of life impairment in patients with chronic spontaneous urticaria.	↑↑	Strong consensus[1] Expert consensus
[1] ≥90% agreement		

Which instruments should be used to assess and monitor disease control in chronic spontaneous urticaria patients?		
We **recommend** the use of the urticaria control test, UCT, and/or the angioedema control test, AECT, for assessing disease control in patients with CSU.	↑↑	Strong consensus[1] Expert consensus
[1] ≥90% agreement		



A

Urticaria Control Test

Patient name: _____ Date: (dd mmm yyyy): ___ ____ _____

Date of birth (dd mmm yyyy): ___ ____ _____

Instructions: You have urticaria. The following questions should help us understand your current health situation. Please read through each question carefully and choose an answer from the five options that *best fits* your situation. Please limit yourself to *the last four weeks*. *Please don't think about the questions for a long time*, and do remember to answer *all questions* and to provide *only one answer to each question.*

1. How much have you suffered from the **physical symptoms of the urticaria (itch, hives (welts) and/or swelling)** in the last four weeks?
   O very much O much O somewhat O a little O not at all
2. How much was your **quality of life** affected by the urticaria in the last 4 weeks?
   O very much O much O somewhat O a little O not at all
3. How often was the **treatment** for your urticaria in the last 4 weeks **not enough** to control your urticaria symptoms?
   O very often O often O sometimes O seldom O not at all
4. **Overall**, how well have you had your urticaria **under control** in the last 4 weeks?
   O not at all O a little O somewhat O well O very well

B

Angioedema Control Test

(AECT)

Patient name: _____ Date: (dd mmm yyyy): ___ ___ _____

Date of birth (dd mmm yyyy): ___ ___ _____

Instructions: You have recurrent swelling referred to as angioedema. Angioedema is a temporary swelling of the skin or mucous membranes which can occur in any part of the body but most commonly involves the lips, eyes, tongue, hands and feet and which can last from hours to days. Some patients develop abdominal angioedema, which is often not visible but painful. Some forms of swelling can also be associated with hives also known as urticaria.

The following four questions assess your current state of health. For each question, please choose the answer from the five options that *best fits your situation*. Please answer *all questions* and please provide *only one answer to each question*.

1. In the last 4 weeks, how often have you had angioedema?
   O very often O often O sometimes O seldom O not at all
2. In the last 4 weeks, how much has your quality of life been affected by angioedema?
   O very much O much O somewhat O a little O not at all
3. In the last 4 weeks, how much has the unpredictability of your angioedema bothered you?
   O very much O much O somewhat O a little O not at all
4. In the last 4 weeks, how well has your angioedema been controlled by your therapy?
   O not at all O a little O somewhat O well O very well

Figure 2. A: The urticaria control test (UCT) and B: the angioedema control test (AECT). Copyright: MOXIE GmbH, Berlin, Germany (www.moxie-gmbh.de)

4.3 The diagnostic work up in CIndU

In patients with CIndU, the routine diagnostic work up should follow the consensus recommendations on the definition, diagnostic testing, and management of CindUs.[34] Diagnostics in CIndU aim to exclude differential diagnoses, to identify the subtype of CIndU, and to determine trigger thresholds.[34] The last of these is important as it allows for assessing disease activity and response to treatment.

For most CIndU subtypes, validated tools for provocation testing are available.[34] Examples include cold and heat urticaria, where a Peltier element-based provocation device (Temp*Test*®) is available,[47] symptomatic dermographism for which a dermographometer (Fric*Test*®) has been developed,[48,49] and delayed pressure urticaria. In cholinergic urticaria, a graded provocation test with office-based methods, e.g. pulse-controlled ergometry, is available.[50,51] Patients with contact urticaria or aquagenic urticaria should be assessed by appropriate cutaneous provocation tests.[34]

Disease control, in patients with CIndU, is assessed by provocation threshold testing and use of the UCT and AECT. Patient-reported outcome measures for disease activity and impact are available for some CindUs.[51,52]

4.4 Diagnosis in Children

Urticaria can occur in all age groups, including infants and young children. Recent reports indicate that, in children, the prevalence of CIndUs and CSU, disease characteristics, underlying causes of CSU, and response to treatment are very similar to those in adults.[53-59]

The diagnostic work up of CSU in children has the same aims as in adults. Differential diagnoses should be excluded with a special focus on cryopyrin-associated periodic syndrome (CAPS). CAPS is a rare disease with a urticaria-like rash that manifests in childhood.[60] If possible, i.e. depending on the age of the child, disease activity, impact and control should be assessed using assessment tools similar to those used in adults, although it has to be noted that no validated disease specific tools for children are available as of now. Triggers of exacerbation should be identified and, where indicated, underlying causes, which appear to be similar to those in adults, should be searched for. In children with CIndU, similar tests for provocation and the determination of trigger thresholds should be performed

5. Management of Urticaria

5.1 Basic considerations

1. The goal of treatment is to treat the disease until it is gone and as efficiently and safely as possible aiming at a continuous UAS7 = 0, complete control and a normalization of quality of life.
2. 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
3. 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 3).

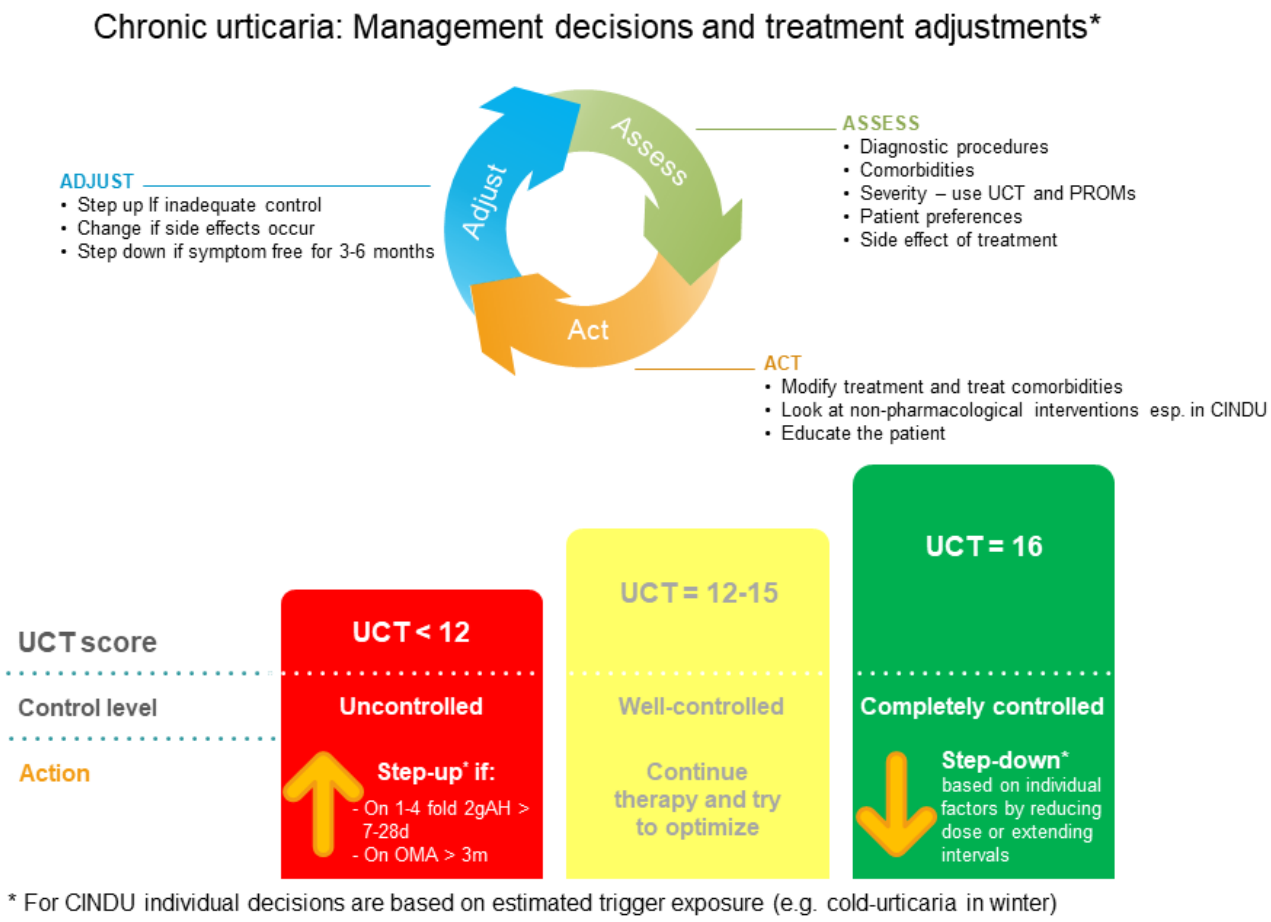


Figure 3. Chronic urticaria: Management decisions and treatment adjustments

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[1] Expert consensus
[1] ≥90% agreement		

5.2 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,[61] 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.[62] In CIndU, avoidance of specific and definite triggers for the development of signs and symptoms, e.g. 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.

5.2.1 Drugs

When these agents are suspected in the course of diagnostic work up, they should be omitted entirely or substituted by another class of agents if indispensable. Drugs causing non-allergic hypersensitivity reactions (the prototypes being NSAIDs) cannot only elicit, but can also aggravate 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 that is suspected to worsen the disease?		
We **recommend** advising patients with chronic spontaneous urticaria to discontinue medication that is suspected to worsen the disease, e.g. NSAIDs.	↑↑	Strong consensus[1] Expert consensus
[1] ≥90% agreement		

5.2.2 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, the exact identification of the range of eliciting wave lengths 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.

5.2.3 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 and bacterial infections of the nasopharynx[63] (even if association with urticaria is not clear in the individual patient and a meta-analysis shows overall low evidence for eradication therapy,[63] *H. pylori* should be eliminated as an association with gastric cancer is suggested[64]). Bowel parasites, a rare possible cause of CSU in developed industrial countries, should be eliminated if indicated.[63,65] In the past, intestinal candidiasis was regarded as a highly important underlying cause of CSU,[63] but more recent findings fail to support a significant causative role.[66] 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.[67,68] Thus it could be shown that successful eradication of helicobacter is only having an impact on CSU if also the subsequent inflammation, i.e gastris and esophagitis is healed.[69] However, similar to infections, it is not easily possible to discern whether any of these are relevant causes of CSU but should be treated as many of them may be also associated with development of malignancies.

5.2.4 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.[70] Further studies are needed to characterize the prevalence and relevance of CSU exacerbation by stress as well as the underlying mechanisms.

5.2.5 Reduction of functional autoantibodies

Direct reduction of functional autoantibodies by plasmapheresis has been shown to be of temporary benefit in some, severely affected patients.[61] 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 may also be reduced by immunosuppressive medication, such as cicloporin.[71]

5.2.6 Food

IgE-mediated food allergy is extremely rarely the underlying cause of CSU.[72,73] If identified, the specific food allergens need to be omitted as far as possible, which leads to a remission within less than 24 hours. 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.[72-77] A pseudoallergen-free diet, containing only low levels of natural as well as artificial food pseudoallergens, has been tested in different countries[78] and also a low histamine diet may improve symptoms in some patients.[79] Those diets are controversial and as yet unproven in well-designed double-blinded placebo-controlled studies. When used they must usually be maintained for a minimum of two to three 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.

5.3 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 three days.[80] However, tolerance induction is only lasting for a few days, thus

a consistent daily exposure to the stimulus just at threshold level is required. Tolerance induction and maintenance are often not accepted by patients, e.g. in the case of cold urticaria where daily cold baths/showers are needed to achieve this.

5.4 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 of these symptomatic treatments is to help patients to 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 H_1-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,[81,82] and their mechanism of action, i.e. their inverse agonist effects on the H_1 receptor, stabilizing its inactive state. Some patients with CIndU can benefit from short term prophylactic antihistamine treatment before relevant trigger exposure.

H_1-antihistamine treatment

H_1-antihistamines have been available for the treatment of urticaria since the 1950s. The older 1st generation H_1-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 GA²LEN position paper[83] it is strongly recommended not to use 1st generation H_1-antihistamines any longer in allergy both for adults and especially in children. This view is shared by the WHO guideline ARIA.[84] Based on strong evidence regarding potentially serious side-effects of 1st generation H_1-antihistamines (lethal overdoses have been reported) we recommend against their use for the routine management of CU as first line agents.

Modern 2nd generation H_1-antihistamines are minimally or non-sedating and free of anticholinergic effects.[85] However, two 2nd generation H_1-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 H_1-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 H_1-antihistamines 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 H_1-antihistamines in urticaria are largely lacking.

Should modern 2nd generation H_1-antihistamines be used as first-line treatment of urticaria?		
We **recommend** a 2nd generation H_1-antihistamine as first-line treatment for all types of urticaria.	↑↑	Strong consensus[1] Evidence- and consensus-based (see Evidence Report)
[1] 100% agreement		

Is an increase in the dose to up to four-fold of modern 2nd generation H_1-antihistamines useful and to be preferred over other treatments in urticaria?		
We **recommend** updosing of a 2nd generation H_1-antihistamine up to 4-fold in patients with chronic urticaria unresponsive to a standard-dosed 2nd generation H_1-antihistamines as second line treatment before other treatments are considered.	↑↑	Strong consensus[1] Evidence- and consensus-based (see Evidence Report)
[1] ≥90% agreement		

Should modern 2nd generation H_1-antihistamines be taken regularly or as needed?		
We **suggest** 2nd generation H_1-antihistamines to be taken regularly for the treatment of patients with chronic urticaria.	↑	Strong consensus[1] Evidence- and consensus-based (see Evidence Report)
[1] ≥90% agreement		

Should different 2nd generation H_1-antihistamines be used at the same time?		
We **suggest against** using different H_1-antihistamines at the same time.	↓	Consensus[1] Evidence- and consensus-based (see Evidence Report)
[1] ≥70% agreement		

Several studies show the benefit of the use of a higher than standard dosed 2nd generation H_1-antihistamines in urticaria patients[86-88] corroborating earlier studies with 1st generation H_1-antihistamines that came to the same conclusion.[89,90] Studies support the use of up to fourfold standard-dosed bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, and rupatadine.[86,87,91-94]

If there is no improvement, should higher than fourfold doses of 2nd generation H_1-antihistamines be used?		
We **recommend against** using higher than 4-fold standard dosed H_1-antihistamines in chronic urticaria	↓↓	Strong consensus[1] Evidence- and consensus-based (see Evidence Report)
[1] ≥90% agreement		

In summary, these studies suggest that some patients with urticaria, who show insufficient response to a standard-dosed 2nd generation H_1-antihistamine, benefit from up-dosing which is preferred over mixing different 2nd generation H_1-antihistamines as their pharmacologic properties are different. We, therefore, recommend to increase the dose up to fourfold, in such patients (Figure 4). Patients need to be informed that 2nd generation H_1-antihistamine updosing is off label and higher than fourfold is not recommended as it has not been tested. However, updosing has been suggested in the guidelines for urticaria since the year 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.

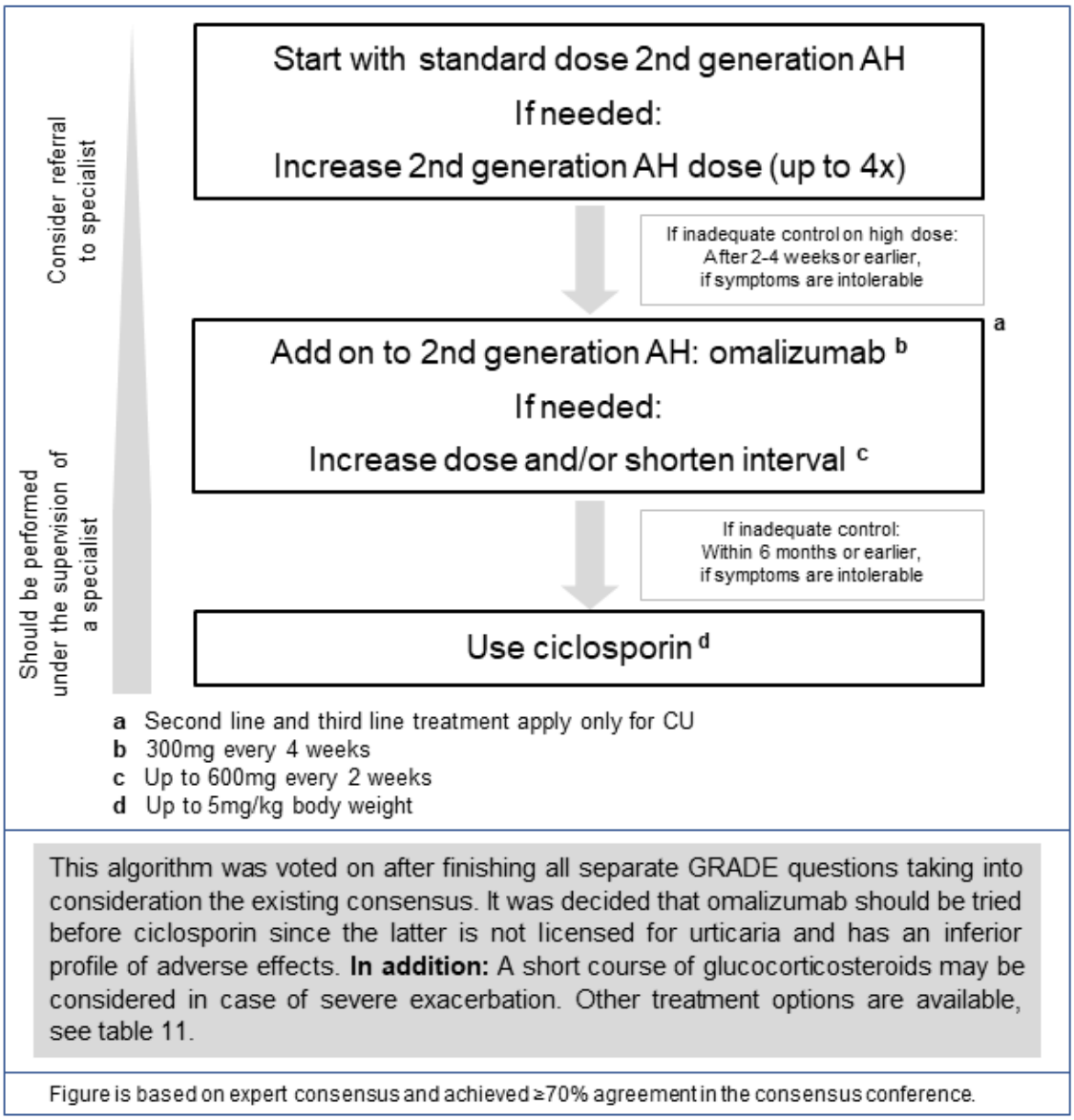


Figure 4. Recommended treatment algorithm for chronic urticaria

Figure 4 legend:

First line = High quality evidence: Low cost and worldwide availability (e.g. modern 2nd generation H_1-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 H_1-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

Omalizumab treatment

Omalizumab is the only other licensed treatment in urticaria for patients who do not show sufficient benefit from treatment with a 2nd generation H_1-antihistamine, and therefore the next step in the algorithm. Omalizumab (anti-IgE) has been shown to be very effective and safe in the treatment of CSU.[95-100] Omalizumab has also been reported to be effective in CIndU[101-103] including cholinergic urticaria,[104] cold urticaria,[105,106] solar urticaria,[107] heat urticaria,[108] symptomatic dermographism,[109,110] as well as delayed pressure urticaria.[111] In CSU, omalizumab prevents wheal and angioedema development,[112] markedly improves quality of life,[113,114] is suitable for long-term treatment,[115] and effectively treats relapse after discontinuation.[115,116] The recommended initial dose in CSU is 300 mg every four weeks. Dosing is independent of total serum IgE.[117]

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.[118-121] Patients need to be informed that omalizumab updosing is off label.

Is omalizumab useful as add-on treatment in patients unresponsive to high doses of H_1-antihistamines?		
We **recommend** adding on omalizumab* for the treatment of patients with CU unresponsive to high dose 2nd generation H_1-antihistamines. *currently licensed for chronic spontaneous urticaria	↑↑	Strong consensus[1] Evidence- and consensus-based (see Evidence Report)
[1] ≥90% agreement		

Ciclosporin treatment

Patients with urticaria who do not show sufficient benefit from treatment with omalizumab, should be treated with ciclosporin 3.5-5mg/kg per day. Ciclosporin is immunosuppressive and has a moderate, direct effect on mast cell mediator release.[122,123] Efficacy of ciclosporin in combination with a modern 2nd generation H_1-antihistamine has been shown in placebo controlled trials[71,124,125] as well as open controlled trials[126] in CSU, but this drug cannot be recommended as standard treatment due to a higher incidence of adverse effects.[124] 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. However, ciclosporin has a far better risk/benefit ratio compared with long-term use of steroids.

Is ciclosporin useful as add-on treatment in patients unresponsive to high doses of H_1-antihistamine?		
We **suggest** using ciclosporin for the treatment of patients with CU unresponsive to high dose of 2nd generation H_1-antihistamine and omalizumab.	↑	Strong consensus[1] Evidence- and consensus-based (see Evidence Report)
[1] ≥90% agreement		

Other symptomatic treatments

Some previous RCTs have assessed the use of leukotriene receptor antagonists. Studies are difficult to compare due to different populations studied, e.g., inclusion of only aspirin and food additive intolerant patients or exclusion of ASST-positive patients. In general, the level of evidence for the efficacy of leukotriene receptor antagonists in urticaria is low but best 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 soles as alternative therapy with low evidence). If systemic corticosteroids are used, doses between 20-50mg/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 specialist clinics. Depending on the country it must be noted that steroids are also not licensed for CU (e.g. in Germany prednisolone is only licensed for acute urticaria). For acute urticaria and acute exacerbations of CSU, a short course of oral corticosteroids, i.e. treatment of a maximum of up to 10 days, may, however, be helpful to reduce disease duration/activity.[127,128] 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[1] Evidence- and consensus-based (see Evidence Report)
We **suggest** considering a short course of rescue systemic glucocorticosteroids in patients with an acute exacerbation of CU.	↑	
[1] ≥90% agreement		

While antihistamines at up to quadruple the manufacturers' recommended dosages will control symptoms in a large part of patients with urticaria in general practice, alternative treatments are needed for the remaining unresponsive patients. It is strongly recommended to stick to the algorithm but it is acknowledged that omalizumab has restrictions due to its high cost and ciclosporin due to its safety profile.

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 three to six months. This is also reflected in Figure 3.

All treatments not listed in the treatment algorithm (Figure 4) are based on clinical trials with low levels of evidence (Table 11).

For H_2-antagonists and dapsone, recommended in the previous versions of the guideline, are now perceived to have little evidence to maintain them as recommendable in the algorithm but they may still have relevance as they are very affordable in some more restricted health care systems. Sulfasalazine, methotrexate, interferon, plasmapheresis, phototherapy, intravenous immunoglobulins (IVIG/IGIV) and other treatment options have low quality evidence or just case series have been published[2] (Table 11). Despite the lack of published evidence, all these drugs may be of value to individual patients in the appropriate clinical context.[129]

Are H_2-antihistamines useful as add-on treatment in patients unresponsive to low or high doses of H_1-antihistamines?		
We **cannot make a recommendation** for or against the combined use of H_1- and H_2-antagonists in patients with chronic urticaria.	**0**	Strong consensus[1] Expert consensus
[1] ≥90% agreement		

Antagonists of tumor necrosis factor alpha (TNF-alpha)[130] and IVIG,[131-134] which have been successfully used in case reports, are recommended currently only to be used in specialized centers as last option (i.e., anti-TNF-alpha for delayed pressure urticaria and IVIG/IGIV for CSU).[135,136]

For the treatment of CSU and symptomatic dermographism, UV-B (narrow band-UVB, TL01), UV-A and PUVA treatment for one to three months can be added to antihistamine treatment[137-139] but caution should be taking regarding the carcinogenic properties of UV light treatment. 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,[140,141] nifedipine in symptomatic dermographism/urticaria factitia[142] and colchicine and indomethacin in delayed pressure urticaria.[143,144] However, more research may be needed for patient subgroups, e.g. recently[145] a pilot study of patients with elevated D-dimer levels showed 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[1] Expert consensus
[1] ≥90% agreement		

Table 11. 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.

Intervention	**Substance (class)**	**Indication**
Widely used		
Antidepressant	Doxepin*	CSU
Diet	Pseudoallergen-free diet**	CSU
H_2-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	Autoimmune CSU

	Rituximab	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

* has also H_1 and H_2-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

5.5 Treatment of special populations

5.5.1 Children

Many clinicians use 1st generation H_1-antihistamines as their first choice treatment of children with urticaria assuming that their safety profile is better known than that of the modern 2nd generation H_1-antihistamines due to a longer experience with them. Also, the use of modern 2nd generation H_1-antihistamines is not licensed for use in children less than six months of age in many countries. However, 1st generation H_1-antihistamines have an inferior safety profile compared with 2nd generation H_1-antihistamines, and are, therefore, not recommended as first line treatment in children with urticaria. 2nd generation H_1-antihistamines with proven efficacy and safety in the pediatric population include bilastine,[146] cetirizine,[147] desloratadine,[148,149] fexofenadine,[150] levocetirizine,[151] loratadine[147] and rupatadine.[152] The choice of which 2nd generation H_1-antihistamines to use in children with urticaria should take into consideration the age and availability as not all are available as syrup or fast dissolving tablet suitable for children. The lowest licensed age also differs from country to country. All further steps should be based on

individual considerations and be taken carefully as up-dosing 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 (e.g. weight adjusted dosage) in children with chronic urticaria	↑	Strong consensus[1] Expert consensus
[1] ≥90% agreement		

5.5.2 Pregnant and lactating women

The same considerations in principle apply to pregnant and lactating women. In general, use of any systemic treatment should generally be avoided in pregnant women, especially in the first trimester. On the other hand, pregnant women have the right to 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 in pregnancy. Regarding treatment, no reports of birth defects in women having used modern 2nd generation H_1-antihistamines during pregnancy have been reported to date. However, only small sample size studies are available for cetirizine[153] and one large meta-analysis for loratadine.[154] Furthermore, as several modern 2nd generation H_1-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 in the beginning of pregnancy, 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 H_1-antihistamines is to prefer loratadine with the possible extrapolation to desloratadine and cetirizine with a possible extrapolation to levocetirizine. All H_1-antihistamines are excreted in breast milk in low concentrations. Use of 2nd generation H_1-antihistamines is advised, as nursing infants occasionally develop sedation from the old 1st generation H_1-antihistamines transmitted in breast milk.

The increased dosage of modern 2nd generation H_1-antihistamines can only be carefully suggested in pregnancy since safety studies have not been done, and with loratadine it must be remembered that this drug is metabolized in the liver which is not the case for its metabolite desloratadine. 1st generation H_1-antihistamines should be avoided.[83] The use of omalizumab in pregnancy has been reported to be safe and to date there is no indication of teratogenicity.[155-

[158] 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 embryo-toxic 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 will have to 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[1] Expert consensus
[1] ≥90% agreement		

6. Need for further research

The panel and participants identified several areas in which further research is needed. These points are summarized in
Table 12.

Table 12. Areas of further research in urticaria

- Global epidemiology, in adults and children
- The socio-economic consequences
- Identification of mast cell/basophil activating factors
- Identification of new histological markers
- Identification of serum biomarkers of urticarial activity/mast cell activation
- Clarification of the role of coagulation/coagulation factors in CSU
- Development of commercially available *in vitro* tests for detecting serum auto-antibodies for anti-IgE and anti-FcεRI
- Evaluation of IgE-auto-antibodies
- Clarification of associated psychiatric /psychosomatic diseases and their impact
- Pathomechanisms in antihistamine-resistant urticaria/angioedema
- Double blind control trials comparing different modern 2nd generation H_1-antihistamines in higher doses in CSU and different subtypes of urticaria
- Safety profile of available treatments, long term pharmacosurveillance
- Multicenter studies on the possible effect of anticoagulants (oral and heparin derivatives) on CSU
- Controlled multicenter trials on the possible effect of add-on of H_2-antihistamines, montelukast, sulfones (dapsone/sulfasalazine), methotrexate, azathioprine
- Development of better treatment options
- Trials and licensing of 2nd generation H_1-antihistamines for the treatment of children below 6 months of age

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GA2LEN-UCARE-Network (www.ga2len-ucare.com).

Endorsing societies: *[will be added after the review phase]*

* endorsed with comments

** the official delegate agreed with the guideline but at time of publication the official letter of endorsement was not received. If received later an update will be published on the GA^{2}LEN website.

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