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The EAACI/GA²LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria.

The 2017 Revision and Update

Endorsed by the following societies: **AAAAI, AAD, AAIITO, ACAAI, AEDV, APAAACI, ASBAI, ASCIA, BAD, BSACI, CDA, CMICA, CSACI, DDG, DDS, DGAKI, DSA, DST, EAACI, EIAS, EDF, EMBRN, ESCD, GA²LEN, IAACI, IADV, JDA, NVvA, MSAI, ÖGDV, PSA, RAACI, SBD, SFD, SGAI, SGD, SIAAIC, SIDeMaST, SPDV, TSD, UNBB, UNEV and WAO**

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AAAAI	American Academy of Allergy, Asthma & Immunology*
AAD	American Academy of Dermatology
AAIITO	Italian Association of Hospital and Territorial Allergists and Immunologists
ACAAI	American College of Allergy, Asthma and Immunology
AEDV	Spanish Academy of Dermatology and Venereology
APAAACI	Asia Pacific Association of Allergy, Asthma and Clinical Immunology
ASBAI	Brazilian Association of Allergy and Immunopathology
ASCIA	Australasian Society of Clinical Immunology and Allergy
BAD	British Association of Dermatologists
BSACI	British Society for Allergy and Clinical Immunology
CDA	Chinese Dermatologist Association
CMICA	Mexican College of Clinical Immunology and Allergy
CSACI	Canadian Society of Allergy and Clinical Immunology
DDG	German Society of Dermatology
DDS	Danish Dermatological Society
DGAKI	German Society of Allergology and Clinical Immunology
DSA	Danish Society for Allergology
DST	Dermatological Society of Thailand
EAACI	European Academy of Allergology and Clinical Immunology
EDF	European Dermatology Forum
EMBRN	European Mast Cell and Basophil Research Network
ESCD	European Society of Contact Dermatitis
GA ² LEN	Global Allergy and Asthma European Network
IAACI	Israel Association of Allergy and Clinical Immunology
IADVL	Indian Association of Dermatologists, Venereologists and Leprologists

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JDA	Japanese Dermatological Association
NVvA	Dutch Society of Allergology
MSAI	Malaysian Society of Allergy and Immunology
ÖGDV	Austrian Society for Dermatology
PSA	Polish Society of Allergology
RAACI	Russian Association of Allergology and Clinical Immunology
SBD	Brazilian Society of Dermatology
SFD	French Society of Dermatology
SGAI	Swiss Society for Allergology and Immunology
SGDV	Swiss Society for Dermatology and Venereology
SIAAIC	Italian Society of Allergology, Asthma and Clinical Immunology
SIDeMaST	Italian Society of Medical, Surgical and Aesthetic Dermatology and Sexual Transmitted Diseases
SPDV	Portuguese Society of Dermatology and Venereology
TSD	Turkish Society of Dermatology
UNBB	Urticaria Network Berlin-Brandenburg
UNEV	Urticaria Network
WAO	World Allergy Organization

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Abstract

This evidence and consensus-based guideline was developed following the methods recommended by Cochrane and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group. The conference was held on December 1st, 2016. It is a joint initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the EU-founded network of excellence, the Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF), and the World Allergy Organization (WAO) with the participation of 48 delegates of 42 national and international societies. This guideline was acknowledged and accepted by the European Union of Medical Specialists (UEMS).

Urticaria is a frequent, mast cell-driven disease, presenting with wheals, angioedema, or both. The lifetime prevalence for acute urticaria is approximately 20%. Chronic spontaneous urticaria and other chronic forms of urticaria are disabling, impair quality of life, and affect performance at work and school. This guideline covers the definition and classification of urticaria, taking into account the recent progress in identifying its causes, eliciting factors and pathomechanisms. In addition, it outlines evidence-based diagnostic and therapeutic approaches for the different subtypes of urticaria.

Abbreviations

AAS	Angioedema activity score
ACE	Angiotensin-converting enzyme
AE-QoL	Angioedema Quality of Life Questionnaire
AGREE	Appraisal of Guidelines Research and Evaluation
AOSD	Adult-onset Still's disease
ARIA	Allergic Rhinitis and Its Impact on Asthma
ASST	Autologous Serum Skin Test
BAT	Basophil activation test
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-Decisions
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
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
sgAH	2nd generation antihistamine
sJIA	Systemic-onset juvenile idiopathic arthritis
TRAPS	Tumor necrosis factor receptor alpha-associated periodic syndrome
UAS	Urticaria activity score
UCT	Urticaria Control Test
UEMS	European Union of Medical Specialists
UV	Ultraviolet
WAO	World Allergy Organization
WHO	World Health Organization

Introduction

This evidence and consensus-based guideline 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 on December 1st, 2016 in Berlin, Germany.

It is a joint initiative of Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the EU-funded network of excellence, the Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF), and the World Allergy Organization (WAO), all of which provided funding for the development of

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this updated and revised version of the EAACI/GA²LEN/EDF/WAO Guideline on urticaria (1-4). There was no funding from other sources.

This revision and update of the guidelines was developed by 44 urticaria experts from 25 countries, all of which are delegates of national and/or international medical societies (Table 1). All of the societies involved endorse this guideline and have supported its development by covering the travel expenses for the participation of their delegate(s) in the consensus conference. The development of this revision and update of the guideline was supported by a team of methodologists led by Alexander Nast and included the contributions of the participants of the consensus conference (see Table 1).

The wide diversity and number of different urticaria subtypes that have been identified reflect, at least in part, our increasing understanding of the causes and eliciting factors of urticaria as well as the molecular and cellular mechanisms involved in its pathogenesis. The aim of this guideline is to provide a definition and classification of urticaria, thereby facilitating the interpretation of divergent data from different centers and areas of the world regarding underlying causes, eliciting factors, burden to patients and society, and therapeutic responsiveness of subtypes of urticaria. Furthermore, this guideline provides recommendations for diagnostic and therapeutic approaches in common subtypes of urticaria. This guideline is a global guideline and takes into consideration that causative factors in patients, medical systems and access to diagnosis and treatment vary in different countries.

Table 1. Guideline development group members

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Methods

The detailed methods used to develop this revision and update of the EAACI/GA²LEN/EDF/WAO guideline on urticaria are published as separate methods report, including all GRADE tables (Insert REF to methods report including DOI).

In summary, this updated and revised 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).

Experts from 42 societies were nominated to be involved in the development of the guideline. First, key questions and relevant outcomes were selected and rated by the experts using an online survey tool (7). Twenty-three key questions were chosen by 30 members of the expert panel.

Subsequently, we developed a literature review protocol, which specified our literature search strategy, researchable questions (PICO), eligibility criteria, outcomes as chosen by the experts, the risk of bias assessment, and strategies for data transformation, synthesis and evaluation.

The systematic literature search was conducted on 1 June 2016 and yielded 8090 hits. Two independent reviewers evaluated the literature and extracted eligible data. After two screening phases, 65 studies were determined to fulfill the inclusion criteria. 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 GRADE using GRADEpro Guideline Development Tool (GDT) (9, 10). Five criteria (namely, risk of bias, inconsistency, indirectness, imprecision and publication bias) were evaluated for each outcome resulting in an overall assessment of quality of evidence (Table 2). Effect measures such as risk ratios express the size of an effect, and the quality rating expresses how much trust one can have in a result.

Table 2: Summary of the GRADE approach to assessing the quality of evidence by outcome (11)

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 modified evidence-to-decisions (EtD) frameworks were created to help the experts make a judgment on the size of the desirable and the undesirable effect, the balance of the two, and to provide an overview of quality. The evidence assessment yielded 31 GRADE

evidence profiles/evidence-to-decision frameworks. A recommendation for each evidence-based key question was drafted using standardized wording (Table 3).

Table 3: Standardized wording and symbols were used to formulate the recommendations

Type of recommendation	Wording	Symbols	Implications
Strong recommendation for the intervention	“We recommend ...”	↑↑	We believe that all or almost all informed people would make that choice. Clinicians will have to spend less time on the process of decision making, and may devote that time to overcome barriers to implementation and adherence. In most clinical situations, the recommendation may be adopted as a policy.
Conditional recommendation for the intervention	“We suggest ...”	↑	We believe that most informed people would make that choice, but a substantial number would not. Clinicians and health care providers will need to devote more time on the process of shared decision making. Policy makers will have to involve many stakeholders and policy making requires substantial debate.
Conditional recommendation for either the intervention of the comparison	“We cannot make a recommendation with respect to ...”	0	At the moment, a recommendation in favour or against an intervention cannot be made due to certain reasons (e. g. no evidence data available, conflicting outcomes, etc.)
Conditional recommendation against the intervention	“We suggest against ...”	↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
Strong recommendation against the intervention	“We recommend against ...”	↓↓	We believe that all or almost all informed people would make a choice against that intervention. This recommendation can be adopted as a policy in most clinical situations.

In a pre-conference online voting round, all GRADE tables EtD frameworks and draft recommendations were presented and voted on. Of the 41 invited participants (expert panel) 30 completed the survey (response rate 73%). The results were either fed back to the expert panel or integrated into the EtD frameworks. All EtD frameworks and draft recommendations were made available to the participants before the consensus conference.

During the conference all recommendations were voted on by over 250 participants, all of whom had to submit a declaration that they were a) a specialist seeing urticaria patients and b) gave a declaration of conflict of interest. A nominal group technique was used to come to an

agreement on the different recommendations (12). The consensus conference followed a structured approach: presentation of the evidence and draft recommendation, open discussion, initial voting or collection of alternative wording and final voting, if necessary. Participants eligible for voting had received one green and one red card, either of which they held up when voting for or against a suggested recommendation. Voting results were documented. Strong consensus was defined as >90% agreement, 70-89% was documented as consensus. All recommendations passed with a 75% agreement. An internal and an external review took place.

All consented recommendations are highlighted in grey and it is indicated whether these are based on expert opinion (based on consensus) or evidence and expert opinion (based on evidence and consensus).

Definition

Definition

Urticaria is a group of diseases 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, 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 in patients with urticaria 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 in urticaria patients 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).

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

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

Acute spontaneous urticaria is defined as the occurrence of spontaneous wheals, angioedema or both for less than 6 weeks.

How should urticaria be classified?		
We recommend that urticaria is classified based on its duration as acute (≤ 6 weeks) or chronic (> 6 weeks).		
We recommend that urticaria is classified as spontaneous (no specific eliciting factor involved) or inducible (specific eliciting factor involved). (consensus-based)	↑↑	> 90% consensus

Table 4 presents a classification of chronic urticaria (CU) subtypes for clinical use. This classification has been maintained from the previous guideline by consensus (>90%) Urticarial vasculitis, maculo-papular cutaneous mastocytosis (formerly called urticaria pigmentosa), 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 such as syndromes that can manifest with wheals and/or angioedema are not considered to be subtypes of urticaria, due to their distinctly different pathophysiologic mechanisms (Table 5).

Should we maintain the current guideline classification of chronic urticaria?		
We recommend that the current guideline classification of chronic urticaria should be maintained. (consensus-based)	↑↑	> 90% consensus

Table 4. Recommended classification of chronic urticaria.

Chronic Urticaria Subtypes	
Chronic Spontaneous Urticaria (CSU)	Inducible Urticaria
Spontaneous appearance of wheals, angioedema 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 Cholinergic urticaria Contact urticaria Aquagenic urticaria
¹ For example, autoreactivity, i.e. the presence of mast cell-activating autoantibodies; ² also called <i>urticaria factitia</i> or dermographic urticaria; ³ also called cold contact urticaria, ⁴ also called pressure urticaria; ⁵ also called heat contact urticaria	

Table 5. Diseases related to urticaria for historical reasons, and syndromes that present with hives and/or angioedema.

- Maculopapular cutaneous mastocytosis (urticaria pigmentosa)
- 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)

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.

Pathophysiological aspects

Urticaria is a mast cell-driven disease. 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 ill defined and likely to be heterogeneous and diverse. 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 virtually always exhibits upregulation of endothelial cell adhesion molecules, neuropeptides and growth factors and a mixed inflammatory perivascular infiltrate of variable intensity, consisting of neutrophils with or without eosinophils, basophils, macrophages, and T-cells but without vessel-wall necrosis, which is a hallmark of urticarial vasculitis (13-17). The nonlesional skin of chronic spontaneous urticaria (CSU) patients shows upregulation of adhesion molecules (18), infiltrating eosinophils, and altered cytokine expression (19). A mild to moderate increase of mast cell numbers has also been reported by some authors. 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).

Burden of disease

The burden of CU for patients, their family and friends, the health care system and society is substantial. 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-QoL), the angioedema quality of life questionnaire (AE-QoL) and the urticaria control test (UCT) in studies and clinical practice has helped to better define the effects and impact of CU on patients (24). The available data indicate that urticaria markedly affects both objective functioning and subjective well-being (25-27). Previously, O'Donnell et al. showed that health status scores in CSU patients are comparable to those reported by patients with coronary artery disease (28). Furthermore, both health status and subjective satisfaction in patients with CSU are lower than in healthy subjects and in patients with respiratory allergy (29). CU also has considerable costs to patients and the society (30-32).

Diagnosis of urticaria

Diagnostic work up in Acute Urticaria

Acute urticaria usually does not require a diagnostic workup, as it is usually self-limiting. The only exception is the suspicion of acute urticaria due to a type I food allergy in sensitized patients or the existence of other eliciting factors such as non-steroidal anti-inflammatory drugs (NSAIDs). In this case, allergy tests as well as educating the patients 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. (consensus-based)	⇓	> 90% consensus

The diagnostic work up in CU

The diagnostic work up of CSU has three major aims: 1) to exclude differential diagnoses, 2) to assess disease activity, impact, and control, and 3) to identify triggers of exacerbation or, where indicated, any underlying causes. Ad 1) Wheals or angioedema can be present in some other conditions, too. In patients who display only wheals (but no 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 only from recurrent angioedema (but not from wheals), bradykinin-mediated angioedema like angiotensin-converting-enzyme (ACE)-inhibitor induced angioedema or other non-mast cell related angioedema, i.e. HAE type 1-3, should be considered as differential diagnoses (Figure 1). Ad 2) Baseline assessment of disease activity (UAS, AAS), quality of life (CU-Q2oL, AE-QoL), and disease control (UCT) are indispensable for guiding treatment decisions, providing better insights into the patients' disease burden, as well as facilitating, improving, and standardizing the increasingly important documentation work (see also section on Assessment of disease activity, impact, and control). Ad 3) History taking is essential in patients with urticaria, as exacerbating triggers are variable. Further diagnostic procedures to reveal underlying causes in patients with longstanding and uncontrolled disease need to be determined carefully.

In the last decades, many advances have been made in identifying causes of different types and subtypes of urticaria, e.g. in CSU (33-35). Among others, autoimmunity mediated by functional autoantibodies directed against the high-affinity IgE receptor or IgE autoantibodies to autoantigens, pseudo-allergy (non-allergic hypersensitivity reactions) to foods or drugs, and acute or chronic infections (e.g. *Helicobacter pylori* or *Anisakis simplex*) have been described as causes of CU (Table 6). However, there are considerable variations in the frequency of underlying causes in the different studies. This also reflects regional differences in the world,

e.g. differences in diets and the prevalence of infections. Thus, it is important to remember that not all possible causative factors need to be investigated in all patients, and the first step in diagnosis is a thorough history, taking the following items into consideration:

1. Time of onset of disease
2. Shape, size, frequency/duration and distribution of wheals
3. Associated angioedema
4. Associated symptoms, e.g. bone/joint pain, fever, abdominal cramps
5. Family and personal history regarding wheals and angioedema
6. Induction by physical agents or exercise
7. Occurrence in relation to daytime, weekends, menstrual cycle, holidays, and foreign travel
8. Occurrence in relation to foods or drugs (e.g. NSAIDs, ACE-Inhibitors)
9. Occurrence in relation to infections, stress
10. Previous or current allergies, infections, internal/autoimmune diseases, gastric/intestinal problems or other disorders
11. Social and occupational history, leisure activities
12. Previous therapy and response to therapy including dosage and duration
13. Previous diagnostic procedures/results

The second step of the diagnosis is the physical examination of the patient. Where it is indicated by history and/or physical examination, further appropriate diagnostic tests should be performed. The selection of these diagnostic measures largely depends on the nature of the urticaria subtype, as summarized in Fig. 1 and Table 6.

Figure 1. Recommended diagnostic algorithm for chronic urticaria

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; RAS: Renin angiotensin system

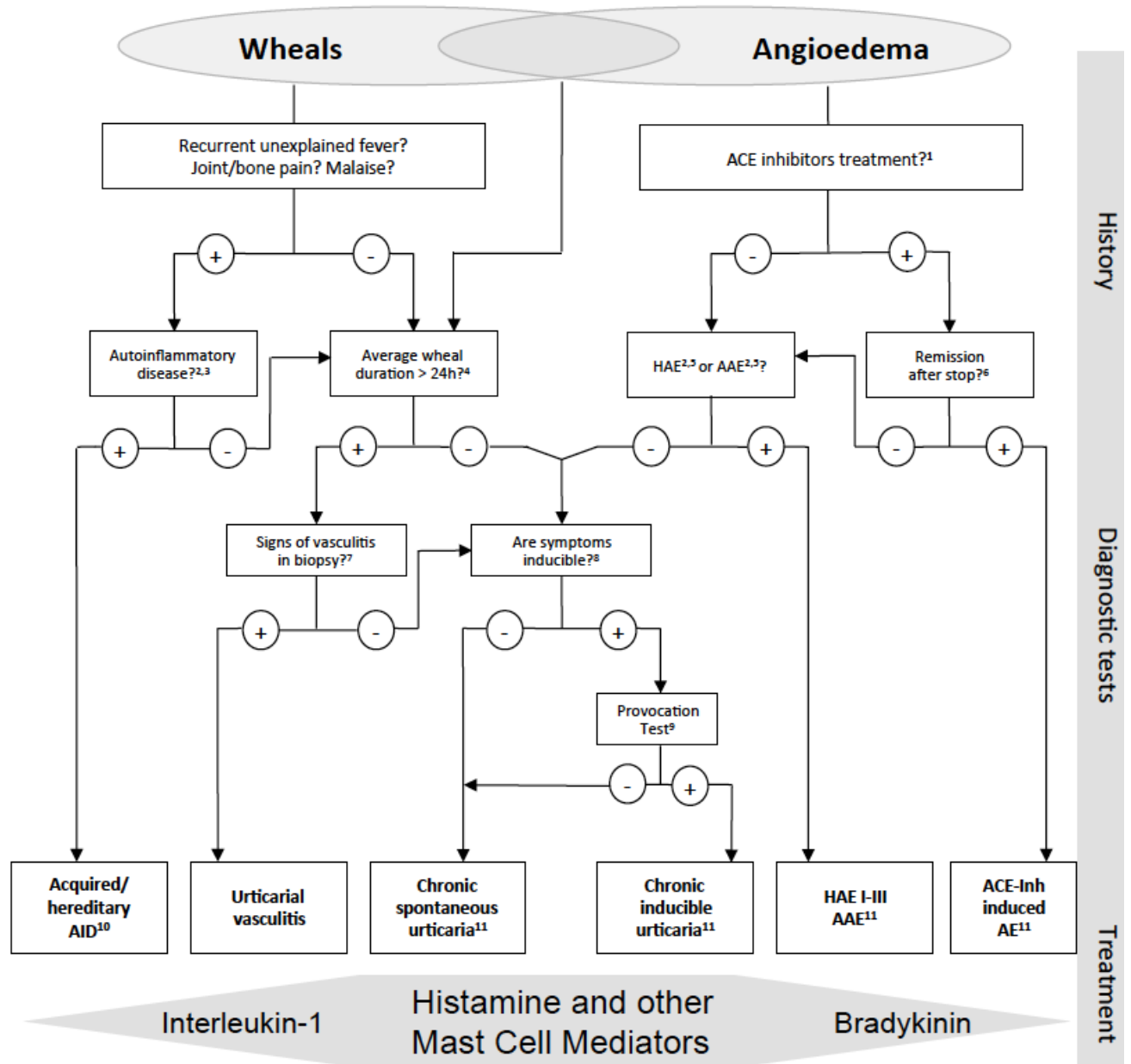


Figure legend

- 1 Apart from ACE inhibitors other renin inhibitors and sartans 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 If there is no remission after 6 months of ACE-inhibitor discontinuation C1-Inhibitor should be tested for.
- 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 come? Can you bring out your wheals?"
- 9 In patients with a history suggestive of inducible urticaria standardized provocation testing according to international consensus recommendations (36) 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.

Table 6. 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	Avoidance of suspected triggers (e.g. drugs); Conduction of diagnostic tests for (in no preferred order): (i) infectious diseases (e.g. <i>Helicobacter pylori</i>); (ii) functional autoantibodies (e.g. autologous skin serum test); (iii) thyroid gland disorders (thyroid hormones and autoantibodies); (iv) allergy (skin tests and/or allergen avoidance test, e.g. allergen-free diet); (v) concomitant CIndU, see below (36)(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 (37)
	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	None

		mixer ⁴	
	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.

¹Depending on suspected cause.

²Unless strongly suggested by patient history, e.g. allergy.

³All tests are done with different levels of the potential trigger to determine the threshold.

⁴For details on provocation and threshold testing see (36)

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.

(consensus-based)

↑↑

**> 90%
consensus**

What routine diagnostic measures should be performed in chronic spontaneous urticaria?

We recommend limited investigations. Basic tests include differential blood count and CRP and/or ESR.

(consensus-based)

In CSU, we recommend performing further diagnostic measures based on the patient history and examination, especially in patients with long standing and/or uncontrolled disease.

↑↑

**> 90%
consensus**

(consensus-based)		
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Should routine diagnostic measures be performed in chronic inducible urticaria?		
We recommend using provocation testing to diagnose chronic inducible urticaria.		
We recommend to use provocation threshold measurements and the UCT to measure disease activity and control in patients with chronic inducible urticaria, respectively.	↑↑	> 90% consensus
(consensus-based)		

Intensive and costly general screening programs for causes of urticaria are strongly advised against. The factors named in Table 6 in the extended programme should only be investigated based on patient history. Type I allergy is an extremely rare cause of CSU. In contrast, pseudo-allergic (non-allergic hypersensitivity reactions) to NSAIDs or food may be more relevant for CSU. Diagnosis should be based on history of NSAID intake or a pseudo-allergic elimination diet protocol. Bacterial, viral, parasitic, or fungal infections, e.g. with *H. pylori*, streptococci, staphylococci, *Yersinia*, *Giardia lamblia*, *Mycoplasma pneumoniae*, hepatitis viruses, *norovirus*, *parvovirus B19*, *Anisakis simplex*, *Entamoeba* spp, *Blastocystis* spp, have been implicated to be underlying causes of urticaria (38-40). The frequency and relevance of infectious diseases varies considerably between different patient groups and different geographical regions. For example, *Anisakis simplex*, a sea fish nematode, has only been discussed as a possible cause of recurrent acute spontaneous urticaria in areas of the world

where uncooked fish is eaten frequently (41, 42). The relevance of *H. pylori*, dental or ear, nose and throat infections also appears to vary between patient groups (40, 43-46). More research is needed in order to make definitive recommendations regarding the role of infection in urticaria.

Routine screening for malignancies in the diagnosis of underlying causes for urticaria is not suggested. Although it is noted that a slightly increased prevalence has been reported in Taiwan (47) there is not sufficient evidence available for a causal correlation of urticaria with neoplastic diseases. Ruling out malignancies is however warranted if patient history (e.g. sudden loss of weight) points to this.

Currently, the only generally available tests to screen for autoantibodies against either IgE or FcεR1 (the high affinity IgE receptor) are the Autologous Serum Skin Test (ASST) and basophil activation tests (BATs). The ASST is a nonspecific screening test that evaluates the presence of serum histamine-releasing factors of any type, not just histamine-releasing autoantibodies. The ASST should be performed with utmost care since infections might be transmitted if, by mistake, patients were injected with someone else's serum. The subject is further elucidated in a separate EAACI/GA²LEN position paper (48, 49).

BATs assess histamine release or upregulation of activation markers of donor basophils in response to stimulation with the serum of CSU patients. BATs can help to co-assess disease activity in patients with urticaria (50, 51) as well as to diagnose autoimmune urticaria (52). Furthermore, BAT can be used as a marker for responsiveness to ciclosporin A or omalizumab (53, 54).

In some subjects with active CSU, several groups have noted blood basopenia and that blood basophils exhibit suppressed IgE receptor-mediated histamine release to anti-IgE. Blood basophils are detected in skin lesions of CSU patients (19). CSU remission is associated with increases in blood basophil numbers and IgE receptor-triggered histamine response (55, 56). A rise in basophil number is also observed during anti-IgE treatment(57) This finding, however, needs to be examined in future research and currently does not lead to diagnostic recommendations. However, it should be noted that a low basophil blood count should not result in further diagnostic procedures. It is also known, that levels of D-dimer are significantly higher in patients with active CSU and decrease according to the clinical response of the disease to omalizumab. The relevance of this finding is not yet clear and currently it is not recommended to measure D-dimer levels (58, 59).

Assessment of disease activity, impact and control

Disease activity in spontaneous urticaria should be assessed both in clinical care and trials with the UAS7 (Table 7), a unified and simple scoring system that was proposed in the last version of the guidelines and has been validated (60, 61). 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 centres. As urticaria activity frequently changes, the overall disease activity is best measured by advising patients to document 24-h 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 patients with angioedema, a novel activity score, the Angioedema Activity Score (AAS) has been developed and validated (62). 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. Recently, the Urticaria Control Test (UCT) has become valuable in the assessment of patients' disease status (63, 64). The UCT was developed and validated to determine the level of disease control in all forms of CU (CSU and CIndU). The UCT has only four items 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 a well-controlled disease is 12 out of 16 possible points. This helps to guide treatment decisions.

Patients should be assessed for disease activity, impact and control at the first and every follow up visit, acknowledging that some tools, e.g. the UAS can only be used prospectively and others, e.g. the UCT, allow for retrospective assessment. Validated instruments such as the UAS7, AAS, CU-Q2oL, AE-QoL and UCT should be used in CU for this purpose.

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. (consensus-based)	↑↑	> 90% consensus

Which instruments should be used to assess and monitor disease activity in chronic spontaneous urticaria patients?		
We suggest 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. (consensus-based)	↑	> 90% consensus
Which instruments should be used to assess and monitor quality of life impairment in chronic spontaneous urticaria patients?		
We suggest 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. (consensus-based)	↑	> 90% consensus
Which instruments should be used to assess and monitor disease control in chronic spontaneous urticaria patients?		
We suggest the use of the urticaria control test, UCT, for assessing disease control in patients with chronic spontaneous urticaria. (consensus-based)	↑	> 90% consensus

In CIndU, the threshold of the eliciting factor(s) should be determined to assess disease activity, e.g. critical temperature and stimulation time thresholds for cold provocation in cold urticaria. These thresholds allow both patients and treating physicians to evaluate disease activity and response to treatment (65-70).

Table 7. The urticaria activity score (UAS7) for assessing disease activity in CSU

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)

Sum of score: 0-6 for each day is summarized over one week (maximum 42)

The diagnostic work up in CIndU

In CIndUs, the routine diagnostic work up should follow the consensus recommendations on the definition, diagnostic testing, and management of CIndUs (36). Diagnostics in CIndU are used to identify the subtype of CIndU and to determine trigger thresholds (36). The latter is important as it allows for assessing disease activity and response to treatment. For most types of CIndU, validated tools for provocation testing are meanwhile available (36). Examples include cold and heat urticaria, where a Peltier element-based provocation device (TempTest®) is available (71), symptomatic dermographism for which a dermatographometer (FricTest®) has been developed (72, 73), and delayed pressure urticaria. In cholinergic urticaria, a graded provocation test with office-based methods, e.g. pulse-controlled ergometry, is available (68, 74). Patients with contact urticaria or aquagenic urticaria should be assessed by appropriate cutaneous provocation tests (36).

Diagnosis in Children

Urticaria can occur in all age groups, including infants and young children. Although data for childhood CSU is still sparse, recent investigations indicate that the prevalence of CIndUs and

CSU, and underlying causes of CSU are very similar to the prevalence and causes in adults, with some minor differences (75-78).

Thus, the diagnostic approaches for children should be similar to those in adults.

The diagnostic work up of CSU in children has the same aims as in adults: 1) 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 (79). 2) 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. 3) 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

Management of Urticaria

Basic considerations

1. The goal of treatment is to treat the disease until it is gone.
2. The therapeutic approach to CU can involve
 - a. the identification and elimination of underlying causes,
 - b. the avoidance of eliciting factors,
 - c. tolerance induction, and/or
 - d. the use of pharmacological treatment to prevent mast cell mediator release and/or the effects of mast cell mediators
3. Treatment should follow the basic principles of treating as much as needed and as little as possible. This may mean stepping up or stepping down in the treatment algorithm according to the course of disease.

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. (consensus-based)	↑↑	> 90% consensus

Identification and elimination of underlying causes and avoidance of eliciting factors

To eliminate an underlying cause, an exact diagnosis is a basic prerequisite. The identification of a cause in CU is, however, difficult in most cases, e.g. infections may be a cause, aggravating factor or unrelated. The only definite proof of a causative nature of a suspected agent or trigger is the remission of symptoms following elimination and recurrence of symptoms following re-challenge in a double-blind provocation test. Spontaneous remission of urticaria can occur any time, the elimination of a suspected cause or trigger can also occur coincidentally.

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 (80), 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. (consensus-based)	↑↑	> 90% consensus

Physical stimuli. Avoidance of physical stimuli for the treatment of CIndUs is desirable, but mostly very difficult to achieve. Detailed information about the physical properties of the respective stimulus should make the patient sufficiently knowledgeable to recognize and control exposure in normal daily life. Thus, for instance, it is important in delayed pressure urticaria and in symptomatic dermographism to point out that pressure is defined as force per area and that simple measures, such as broadening of the handle of heavy bags for pressure urticaria or reducing friction in case of symptomatic dermographism, 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.

Eradication of infectious agents and treatment of inflammatory processes. In contrast to CIndU, CSU is often reported to be associated with a variety of inflammatory or infectious diseases. This is regarded as significant in some instances, but some studies show conflicting results and have methodological weaknesses. These infections, which should be treated appropriately, include those of the gastrointestinal tract like *H. pylori* infection or bacterial infections of the nasopharynx (81) (even if association with urticaria is not clear in the individual patient and a meta-analysis shows overall low evidence for eradication therapy (81), *H. pylori* should be eliminated as an association with gastric cancer is suggested (82)). Bowel parasites, a rare possible cause of CSU in developed industrial countries, should be eliminated if indicated (81, 83). In the past, intestinal candidiasis was regarded as a highly important underlying cause of CSU (81), but more recent findings fail to support a significant causative role (84). Apart from infectious diseases, chronic inflammatory processes due to diverse other diseases have been identified as potentially triggering CSU. This holds particularly for gastritis, reflux oesophagitis or inflammation of the bile duct or gall bladder (85, 86). 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.

Reduction of physical and emotional stress. Although the mechanisms of stress-induced exacerbation are not well investigated, some evidence indicates that disease activity and severity are correlated with stress levels (87). This holds true for emotional stress as well as physical stress which in some entities can be relevant for the development of symptoms such as in cholinergic urticaria (88).

Reduction of functional autoantibodies. Direct reduction of functional autoantibodies by plasmapheresis has been shown to be of temporary benefit in some, severely affected patients (89). 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.

Dietary management. IgE-mediated food allergy is extremely rarely the underlying cause of CSU (90, 91). 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 (90-95). A pseudoallergen-free diet, containing only low levels of natural as well as artificial food pseudoallergens, has been tested in different countries (96) and also a low histamine diet may improve symptoms in those patients (97). Those diets are controversial and as yet unproven in well designed double blinded placebo controlled studies. However, when used they must usually be maintained for a minimum of 2-3 weeks before beneficial effects are observed. However, it should be pointed out that 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 effect of natural and artificial ingredients of food in causing urticaria.

Inducing tolerance

Inducing tolerance can be useful in some subtypes of urticaria. Examples are cold urticaria, cholinergic urticaria, and solar urticaria, where even a rush therapy with UV-A has been proven to be effective within 3 days (98). 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

Symptomatic pharmacological treatment

A basic principle of the pharmacological treatment is to aim at complete symptom relief. Another general principle in pharmacotherapy is to use as much as needed and as little as possible. The extent and selection of medication may therefore vary in the course of the disease.

The main option in therapies aimed at symptomatic relief is to reduce the effect of mast cell mediators such as histamine, PAF and others on the target organs. Many symptoms of urticaria are mediated primarily by the actions of histamine on H₁-receptors located on endothelial cells (the wheal) and on sensory nerves (neurogenic flare and pruritus). Thus, continuous treatment with H₁-antihistamines is of eminent importance in the treatment of urticaria (safety data are available for use of several years continuously). Continuous use of H₁-antihistamines in CU is supported not only by the results of clinical trials (99, 100) but also by the mechanism of action of these medications, i.e. that they are inverse agonists with

preferential affinity for the inactive state of the histamine H₁-receptor and stabilize it in this conformation, shifting the equilibrium towards the inactive state.

However, other mast cell mediators (PAF, leukotrienes, cytokines) can also be involved and a pronounced cellular infiltrate including basophils, lymphocytes and eosinophils may be observed (101). These may respond completely to a brief burst of corticosteroid and may be relatively refractory to antihistamines.

These general considerations on pharmacotherapy refer to all forms of acute and chronic urticaria. The difference between spontaneous urticaria and CIndU is however that in some forms of physical urticaria e.g. cold urticaria instead of continuous treatment on demand treatment may be useful. Especially if the patient knows of a planned trigger such as expected cold exposure when going for a swim in summer the intake of an antihistamine 2 hours prior to the activity may be sufficient.

Antihistamines have been available for the treatment of urticaria since the 1950s. The older first generation antihistamines have pronounced anticholinergic effects and sedative actions on the central nervous system (CNS) and many interactions with alcohol and drugs affecting the CNS, 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 (102) it is strongly recommended not to use first generation antihistamines any longer in allergy both for adults and especially in children. This view is shared by the WHO guideline ARIA (103). Based on strong evidence regarding potential serious side-effects of old sedating antihistamines (lethal overdoses have been reported) we recommend against the use of these sedating antihistamines for the routine management of CU as first line agents, except for the rare places worldwide in which modern 2nd generation antihistamines are not available. The side-effects of first generation H₁-antihistamines are most pronounced for promethazine, diphenhydramine, ketotifen and chlorphenamine and are well-understood. They penetrate the blood-brain barrier, bind to H₁-receptors in the CNS and interfere with the neurotransmitter effects of histamine. Positron-emission tomography (PET) studies document their penetration into the human brain and provide a new standard whereby CNS H₁-receptor occupancy can be related directly to effects on CNS function (104).

The development of modern 2nd generation antihistamines led to drugs which are minimally or non-sedating and free of anticholinergic effects. However, two of the earlier modern 2nd generation drugs, astemizole and terfenadine, which were essentially pro-drugs requiring

hepatic metabolism to become fully active, had cardiotoxic effects if this metabolism was blocked by concomitant administration of inhibitors of the cytochrome P450 (CYP) 3A4 isoenzyme, such as ketoconazole or erythromycin. These two drugs are no longer available in most countries and we recommend that they are not used.

Further progress with regard to drug safety has been achieved in the last few decades with a considerable number of newer modern 2nd generation antihistamines (104). Not all antihistamines have been tested specifically in urticaria, but many non-sedating antihistamines studies are available, e.g. cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, ebastine, rupatadine and bilastine. Modern 2nd generation antihistamines should be considered as the first line symptomatic treatment for urticaria because of their good safety profile. However, up to date, well designed clinical trials comparing the efficacy and safety of modern 2nd generation H₁-antihistamines in urticaria are largely lacking.

Are 2nd H₁-antihistamines to be preferred over 1st generation H₁-antihistamines for the treatment of chronic urticaria?		
We suggest 2nd generation H₁-antihistamines over 1st generation H₁-antihistamines for the treatment of patients with chronic urticaria. (evidence-based and consensus-based)	↑	> 90% consensus
Should modern 2nd generation H₁-antihistamines be used as first-line treatment of urticaria?		
We recommend 2nd generation H₁-antihistamines as first-line treatment of chronic urticaria. (evidence-based and consensus-based)	↑↑	> 90% consensus
Should modern 2nd generation H₁-antihistamines be taken regularly or as needed by patients with chronic urticaria?		
We suggest 2nd generation H₁-antihistamines to be taken regularly for the treatment of patients with chronic urticaria. (evidence-based and consensus-based)	↑	> 90% consensus

Should different 2nd H₁-antihistamines be used at the same time?		
We recommend against using different H₁-antihistamines at the same time. (consensus-based)	⇓	> 90% consensus

There are studies showing the benefit of a higher dosage of 2nd generation antihistamines in individual patients (105-107) corroborating earlier studies which came to the same conclusion employing first generation antihistamines (108, 109). This has been verified in studies using up to fourfold higher than recommended doses of bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, and rupatadine (105, 106, 110-113) .

In summary, these studies suggest that the majority of patients with urticaria not responding to standard doses will benefit from up-dosing of antihistamines. Modern 2nd generation antihistamines at licensed doses are first line treatment in urticaria and up dosing is second line treatment (Fig. 2).

Is an increase in the dose to fourfold of modern 2nd generation H₁-antihistamines useful and to be preferred over other treatments in urticaria (second-line treatment)?		
We suggest up dosing 2nd generation H₁-antihistamines up to 4-fold in patients with chronic urticaria unresponsive to 2nd generation H₁-antihistamines 1-fold. (evidence-based and consensus-based)	↑	> 90% consensus
If there is no improvement, should higher than fourfold doses of 2nd generation H₁-antihistamines be used?		
We recommend against using higher than 4-fold standard dosed H₁-antihistamines in chronic urticaria. (consensus-based)	⇓	> 90% consensus

Further therapeutic possibilities for antihistamines-refractory patients

Omalizumab (anti-IgE) has been shown to be very effective and safe in the treatment of CSU (114-119). Omalizumab has also been reported to be effective in CIndU (120, 121) including cholinergic urticaria (122), cold urticaria (70, 123), solar urticaria (124), heat urticaria (125), symptomatic dermographism (69, 126), as well as delayed pressure urticaria (127). In CSU, omalizumab prevents angioedema development (128), markedly improves quality of life (8, 129), is suitable for long-term treatment (130), and effectively treats relapse after discontinuation (130, 131). Omalizumab, in CU, is effective at doses from 150 – 300 mg per month. Dosing is independent of total serum IgE (132). The recommended dose in CSU is 300 mg every four weeks. The licensed doses and treatment duration vary between different countries.

Is omalizumab useful as add-on treatment in patients unresponsive to high doses of H₁-antihistamines (third-line treatment of urticaria)?		
We recommend adding on omalizumab* for the treatment of patients with CU unresponsive to 2nd generation H₁-antihistamines. (evidence-based and consensus-based) * currently licensed for urticaria	↑↑	> 90% consensus

Ciclosporin A also has a moderate, direct effect on mast cell mediator release (133, 134). Efficacy of ciclosporin A in combination with a modern 2nd generation H₁-antihistamine has been shown in placebo controlled trials (135-137) as well as open controlled trials (138) in CSU, but this drug cannot be recommended as standard treatment due to a higher incidence of adverse effects (136). Ciclosporin A 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 A has a far better risk/benefit ratio compared with long-term use of steroids.

Is ciclosporin A useful as add-on treatment in patients unresponsive to high doses of H₁-antihistamines (third-line treatment of urticaria)?

We suggest adding on ciclosporin A for the treatment of patients with CU unresponsive to 2nd generation H₁-antihistamines.

(evidence-based and consensus-based)

↑

**> 90%
consensus**

Comment by the authors: as shown in the consensus-based treatment algorithm (Figure 2), which was voted on later, it was decided that omalizumab should be tried before ciclosporin A since the latter is not licensed for urticaria and has an inferior profile of adverse effects.

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.

Are leukotriene antagonists useful as add-on treatment in patients unresponsive to high doses of H₁-antihistamines?

We cannot make a recommendation with respect to montelukast as add-on treatment to H₁-antihistamines in patients with chronic urticaria unresponsive to H₁-antihistamines.

(evidence-based and consensus-based)

0

**> 90%
consensus**

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 for prednisone are required with obligatory side effects on long-term use. There is a strong recommendation against the long-term 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 (139, 140). 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. (consensus-based)	⇓	> 90% consensus
We suggest considering a short course of systemic glucocorticosteroids in patients with an acute exacerbation of CU. (consensus-based)	↑	> 90% consensus

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. Before changing to an alternative therapy, it is recommended to wait for 1–4 weeks to allow full effectiveness.

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.

Except for omalizumab and ciclosporin A, which both have restrictions due to their high cost, many of the alternative methods of treatment, such as combinations of modern 2nd generation H₁-antihistamines with leukotriene receptor antagonists, are based on clinical trials with low levels of evidence (Table 9). Based on the level of evidence the recommended third line and fourth line treatment options are thus limited (see algorithm fig.2).

For H₂-antagonists and dapsons, 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 9). Despite the lack of published

evidence, all these drugs may be of value to individual patients in the appropriate clinical context (141)

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-antagonists in patients with chronic urticaria. (evidence-based and consensus-based)	0	> 75% consensus

Antagonists of tumor necrosis factor alpha (TNF-alpha) (142) and IVIG/IGIV (143-146), 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) (147, 148).

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 (149-151).

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 (152, 153), nifedipine in symptomatic dermographism/urticaria factitia (154) and colchicine and indomethacin in delayed pressure urticaria (155, 156). However, more research may be needed for patient subgroups, e.g recently (157) 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 as third-line treatment in urticaria?		
We cannot make a recommendation with respect to further treatment options. (evidence-based and consensus-based)	0	> 90% consensus

Treatment of special populations

Children

Many clinicians use first generation, sedating H₁-antihistamines as their first choice in the treatment of children with allergies assuming that the safety profile of these drugs 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 less than 6 months of age in many countries while the recommendation for the first generation H₁-antihistamines is sometimes less clear since these drugs were licensed at a time when the code of good clinical practice for the pharmaceutical industry was less stringent. As a consequence many doctors choose first generation antihistamines which, as pointed out above, have a lower safety profile compared with modern 2nd generation H₁-antihistamines. A strong recommendation was made by the panel to discourage the use of first generation antihistamines in infants and children. Thus, in children the same first line treatment and up-dosing (weight and age adjusted) is recommended as in adults. Only medications with proven efficacy and safety in the paediatric population should be used. Cetirizine (158), desloratadine (159, 160), fexofenadine (161), levocetirizine (162), rupatadine (163), bilastine (164) and loratadine (158) have been well studied in children and their long-term safety has been well established in the paediatric population. In addition, the choice of the modern 2nd generation H₁-antihistamines in children depends on 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 in children with chronic urticaria. (consensus-based)	↑	> 90% consensus

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 occurring in urticaria have also not been studied in pregnancy. Regarding treatment, no reports of birth defects in women having used modern 2nd generation antihistamines during pregnancy have been reported to date. However, only small sample size studies are available for cetirizine (165) and one large meta-analysis for loratadine (166). Furthermore, as several modern 2nd generation 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 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 second-generation H₁-antihistamines is advised, as nursing infants occasionally develop sedation from the old first-generation H₁-antihistamines transmitted in breast milk.

The increased dosage of modern 2nd generation 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. First generation H₁-antihistamines should be avoided (102). The use of omalizumab in pregnancy has been proven to be safe and to date there is no indication of teratogenicity (167-169). 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 reevaluated according to the current recommendations published by regulatory authorities.

Should the same treatment algorithm be used in pregnant women and during lactation?		
<p>We suggest using the same treatment algorithm with caution both in pregnant and lactating women after risk benefit assessment. Drugs contraindicated in pregnancy should not be used.</p> <p>(consensus-based)</p>	↑	> 90% consensus

Need for further research

The panel and participants identified several areas in which further research is needed. These points are summarized in Table 8.

Table 8. 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
- Determination of minimal important differences for instruments that assess disease activity or impact relevant response (e.g. UAS, CU-Q2oL)
- 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 or 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 H₁-antihistamines in higher doses in CSU and different subtypes of urticaria
- Regular versus on demand use of H₁-antihistamines on the duration of urticaria / severity of urticaria
- Safety profile of available treatments, long term phamacosurveillance
- Multicentre studies on the possible effect of anticoagulants (oral and heparin derivatives) on CSU
- Controlled multicenter trials on the possible effect of add-on of H₂-antihistamines, montelukast, sulfones (dapson/sulfasalazine), methotrexate, azathioprine

Acknowledgement

Important: As this is a global 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.

Physicians and specialists who contributed to the development of this revision and update of the guidelines by active participation in the democratic process and discussion within the 5th International Consensus Meeting on Urticaria 2016.

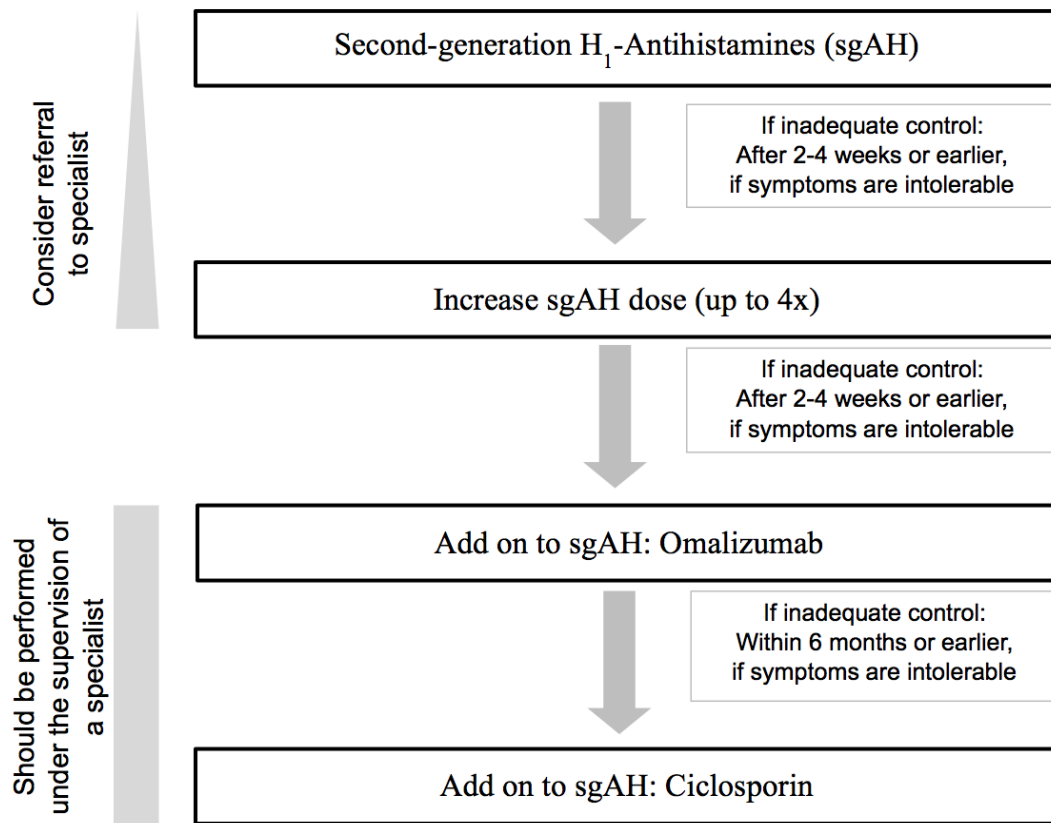
All national societies for funding their delegates.

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

Figures

Figure 2. Recommended treatment algorithm for urticaria*



Chronic urticaria treatment algorithm. This algorithm was voted on after finishing all separate GRADE questions taking into consideration the existing consensus. It was decided that omalizumab should be tried before ciclosporin A since the latter is not licensed for urticaria and has an inferior profile of adverse effects. **In addition:** A short course of glucocorticosteroids may be considered in case of severe exacerbation. Other treatment options are available, see table 9. **> 90% consensus**

First line = High quality evidence: Low cost and worldwide availability (e.g. modern 2nd generation 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 = high quality evidence: Low cost, good safety profile, good efficacy

Third line as add on to antihistamine

Omalizumab = High quality evidence: High cost, very good safety profile, very good efficacy

Fourth line as add on

Ciclosporin A = 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

Table 9. 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.

<i>Widely used</i>		
Intervention	Substance (class)	Indication
Antidepressant	Doxepin*	CSU
Diet	Pseudoallergen-free diet**	CSU
H ₂ -antihistamine	Ranitidine	CSU
Immunosuppressive	Methotrexate	CSU +/- DPU***

	Mycophenolate mofetil	Autoimmune CSU
Leukotriene receptor antagonist	Montelukast	CSU, DPU
Sulphones	Dapsone,	CSU +/- DPU
	Sulphasalazine	CSU +/- DPU
<i>Infrequently used</i>		
Anabolic steroid	Danazol	Cholinergic urticaria
Anticoagulant	Warfarin	CSU
Antifibrinolytic	Tranexamic acid	CSU with angioedema
Immunomodulator	IVIG	Autoimmune CSU
	Plasmapheresis	Autoimmune CSU
Miscellaneous	Autologous blood/serum	CSU
	Hydroxychloroquine	CSU
Phototherapy	Narrow-band UVB	Symptomatic dermographism
Psychotherapy	Holistic medicine	CSU
<i>Rarely used</i>		
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

<i>Very rarely used</i>		
Immunosuppressive	Tacrolimus	CSU
Miscellaneous	Vitamin D	CSU
	Interferon alpha	CSU

Legend:

* has also H₁ and H₂-antihistaminergic properties

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

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

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