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GUIDELINE

S3 Guideline Urticaria. Part 1: Classification and diagnosis of urticaria – German-language adaptation of the international S3 Guideline

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

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

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

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

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

GD – Gesellschaft für Dermatopharmazie (Society for Dermatopharmaceutics)

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

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

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

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Summary

The lifetime prevalence of urticaria, a severe allergic disease, is almost 20%. It not only limits the quality of life of those affected, but also their general performance at work and in their daily activities. This publication is the first section of the Urticaria Guideline. It covers the classification and diagnosis of urticaria, taking into account the major advances in research into its causes, triggering factors and pathomechanisms. It also addresses strategies for the efficient diagnosis of the different subtypes of urticaria. This is crucial for individual, patient-oriented treatment, which is covered in the second part of the guideline, published separately. This German-language guideline was developed according to the criteria of the AWMF on the basis of the international English-language S3 guideline with special consideration of health system characteristics in the German-speaking countries.

This first part of the guideline describes the classification of urticaria, distinguishing spontaneously occurring wheals (hives) and angioedema from forms of urticaria with inducible symptoms. Urticaria is defined as sudden onset of wheals, angioedema, or both, but is to be distinguished from conditions in which wheals occur as a short-term symptom, such as anaphylaxis. The diagnosis is based on (a limited number of) laboratory tests, but especially on medical history. In addition, validated instruments are available to measure the severity, activity and course of the disease.

KEYWORDS
angioedema, diagnostics, guideline, urticaria, wheal

INTRODUCTION

Urticaria is a common disease, triggered by mast cells and characterized by wheals, angioedema, or both. Lifetime prevalence of urticaria is almost 20%. Chronic urticaria (or more precisely chronic spontaneous urticaria as well as chronic inducible urticaria) leads to decreased quality of life and decreased performance at work or at school.

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

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

Part 1 of the guideline describes the classification of urticaria, differentiating spontaneously occurring wheals and edemas from urticaria types with inducible symptoms. Urticaria is defined as the sudden occurrence of wheals, angioedema, or both. It needs to be differentiated from

TABLE 1 Recommendation strengths – wording, symbols and interpretation

Strength of Recommendation	Wording	Symbol	Interpretation
Strong recommendation for the use of an intervention	"We recommend …"	↑↑	We believe that all or almost all informed people would make a choice in favor of using this intervention. Clinicians will not have to spend as much time on the process of decision-making with the patient and may devote that time instead to overcoming barriers to implementation and adherence. In most clinical situations, the recommendation can be adopted as a policy.
Weak recommendation for the use of an intervention	"We suggest …"	↑	We believe that most informed people would make a choice in favor of using this intervention, but a substantial number would not. Clinicians and other healthcare providers will need to devote more time to the process of shared decision-making. Policy makers will have to involve many stakeholders and policy making will require substantial debate.
No recommendation with respect to an intervention	"We cannot make a recommendation with respect to…"	0	Currently, a recommendation in favor of or against using this intervention cannot be made due to certain circumstances (e.g., unclear or balanced benefit-risk ratio, no data available).
Weak recommendation against the use of an intervention	"We suggest against …"	↓	We believe that most informed people would make a choice against using this intervention, but a substantial number would not.
Strong recommendation against the use of an intervention	"We recommend against…"	↓↓	We believe that all or almost all informed people would make a choice against using this intervention. This recommendation can be adopted as a policy in most clinical situations.

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

conditions with wheals occurring only as a short-term symptom, such as anaphylaxis. Diagnostics are based on (limited) laboratory investigations, but in particular on the medical history. There are also validated instruments for recording severity, activity, and progression.

METHODS

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

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

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

TABLE 2 Classification of strength of consensus

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

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

Example of a recommendation with standardized guideline wording and symbols:

We recommend that …	↑↑	Strong consensus, expert consensus

Consensus procedure

A German translation of the English-language S3 guideline "*The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria*" by Zuberbier et al. (2021)[1] was read by all experts. In an online Delphi procedure, the

background texts were pre-approved in sections, and the recommendations item by item. Comments were collected and compiled by the *Methods* group, then referred back to the experts. Amended drafts were then subjected to final discussion and consensus in an online consensus meeting on 25th October 2021, moderated by Prof. Dr. Alexander Nast, AMWF guideline counselor and methodical coordinator. Essentially, all recommendations were adopted from the international guideline. Minor deviations in the wording resulted for translation-related reasons or because the respective recommendation had to be adapted to the health care setting in Germany (such as the addition of a note on off-label use; for further details, see the guideline report).

External review / Approval by the professional societies / Implementation

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

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

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

Updates / Validity

This guideline is valid until 31.01.2025.

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

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

DEFINITION OF URTICARIA

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 features of a spectrum of clinical conditions, for example, anaphylaxis, autoinflammatory syndromes, urticarial vasculitis, or bradykinin-mediated angioedema including hereditary angioedema (HAE).

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

A. A wheal has three typical features:
   1. a sharply circumscribed superficial central swelling of variable size and shape, 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 min to 24 h.

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

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 according to its duration as acute or chronic, and according to the role of definite triggers as inducible or spontaneous. Acute urticaria is defined as the occurrence of wheals, angioedema, or both for 6 weeks or less. Chronic urticaria is defined as the occurrence of wheals, angioedema, or both for more than 6 weeks. Chronic urticaria can come with daily or almost daily signs and symptoms or an intermittent/recurrent course. Chronic spontaneous urticaria (CSU) may recur after months or years of full remission.

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

TABLE 3 Recommended classification of chronic urticaria

Subtypes of chronic urticaria	
Chronic spontaneous urticaria (CSU)	**Chronic inducible urticaria (CIndU)**
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[6] Cholinergic urticaria Contact urticaria Aquagenic urticaria

[1]For example, type I autoimmunity (autoallergy), IgE against autoantigens, 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 (chronic spontaneous urticaria, CSU) and (chronic inducible urticaria, 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.

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 cold-induced cholinergic 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, that is, 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).	↑↑	Consensus, expert consensus
We **recommend** that urticaria is classified as spontaneous (no definite eliciting factor involved) or inducible (specific definite factor involved).	↑↑	

Table 3 shows the classification of chronic urticaria (CU) subtypes for clinical use. This classification has been taken on and maintained from the preceding international urticaria guideline.

TABLE 4 Examples of diseases historically associated with urticaria, and syndromes associated with wheals and/or angioedema

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.

- Maculopapular cutaneous mastocytosis (urticaria pigmentosa) and indolent systemic mastocytosis with involvement of the skin
- Mast cell activation syndrome (MCAS)
- Urticarial vasculitis
- Bradykinin-mediated angioedema (such as hereditary angioedema, HAE)
- Exercise-induced anaphylaxis
- Cryopyrin-associated periodic syndrome, CAPS (urticarial rash, recurrent fever attacks, arthralgia or arthritis, eye inflammations, fatigue and headaches), that is, familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), or Neonatal Onset Multisystem Inflammatory Disease (NOMID).
- Schnitzler syndrome (recurrent urticarial rash and monoclonal gammopathy, recurrent fever attacks, bone and muscle pain, arthralgia or arthritis and lymphadenopathy)
- Gleich syndrome (episodic angioedema with eosinophilia)
- Wells syndrome (granulomatous dermatitis with eosinophilia/eosinophilic cellulitis)
- Bullous pemphigoid (per-bullous stage)
- Adult-onset Still's disease (AOSD)

Should the classification of chronic urticaria from the international guideline be maintained?

We recommend that the classification of chronic urticaria used in the preceding international guideline should be maintained.	↑↑	Strong consensus, expert consensus

Urticarial vasculitis, maculopapular cutaneous mastocytosis (formerly called urticaria pigmentosa) and indolent systemic mastocytosis with involvement of the skin, mast cell activation syndrome (MCAS), autoinflammatory syndromes (for example, cryopyrin-associated periodic syndromes or Schnitzler's syndrome), non-mast cell mediator-mediated angioedema (for example, 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 4).

Pathophysiological aspects

Urticaria is a predominantly mast cell-driven disease.[4] 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

T cell-driven cytokines and 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. 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.[5–9] The nonlesional skin of chronic spontaneous urticaria (CSU) patients shows upregulation of adhesion molecules, infiltrating eosinophils, altered cytokine expression,[10] and sometimes a mild-to-moderate increase of mast cell numbers.[4] 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.[11–13] 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 biomarkers for different subtypes of urticaria and for distinguishing urticaria from other conditions is desirable.[14]

Burden of disease

The burden of CU for patients, their family and friends, the healthcare system and society is substantial.[15–18] 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, developed specifically for CU), 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.[19] The available data indicate that urticaria markedly affects both objective functioning and subjective well-being.[20–22] Previously, O'Donnell et al. showed that health status scores in CSU patients are comparable to those reported by patients with coronary artery disease.[23] Furthermore, both health status and subjective satisfaction in patients with CSU are lower than in healthy subjects and in patients with respiratory allergy.[24] CU also comes with considerable costs for patients and society.[16–18]

DIAGNOSIS OF URTICARIA

Detailed history taking is essential in urticaria; it is the first step in the diagnostic workup of all urticaria patients. Questionnaires may be useful in this context. 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 workup, with limited tests (see Table 5; 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 5; extended diagnostic program). The aims of all diagnostic tests performed should be clear to the physician and patient.

Diagnostic workup in acute urticaria

Acute urticaria, because it is self-limiting, usually does not require a diagnostic workup apart from anamnesis for possible trigger factors. A targeted medical history is important and may bring about helpful diagnostic procedures. If acute urticaria due to a type I food allergy in sensitized patients or drug hypersensitivity is suspected, especially for non-steroidal anti-inflammatory drugs (NSAIDs), allergy tests and patient education may be useful to allow patients to avoid re-exposure to relevant causative factors. The typical differentiator between acute urticaria and type-I allergic reactions, for example in food allergies, is the time course. Reactions will typically occur within 30 minutes after ingestion of the respective foods, and will disappear on their own after a few hours. If wheals reappear on the next morning without ingestion of food, this is not typical for IgE mediated allergy.

Should routine diagnostic measures be performed in acute urticaria?

We **recommend against** any routine diagnostic measures in acute spontaneous urticaria.	↓↓	Consensus, expert consensus

Diagnostic workup in CSU

In CSU, the diagnostic workup 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 6).[26]

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.

TABLE 5 Recommended diagnostic tests in frequent urticaria subtypes

Form of urticaria	Subtype	Recommended routine diagnostics	Extended diagnostic program[1] (based on the history) for identification of 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 (such as drugs); diagnostic tests for (in no preferred order): (i) Infectious diseases (such as *helicobacter pylori*) (ii) Chronic rhinosinusitis (iii) Functional autoantibodies (such as basophil activation test) (iv) Thyroid diseases (thyroid hormones and autoantibodies) (v) Allergy (skin tests and/or allergen avoidance tests such as avoidance diet) (vi) Concomitant CIndU, see below[34] (vii) Severe systemic diseases (such as tryptase) (viii) Other (such as 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 wavelengths and threshold test[3]	Rule out other light-induced dermatoses
	Symptomatic dermographia	Triggering of dermographia and threshold test[3,4]	Differential blood count, ESR or CRP
Other types of urticaria	Vibratory angioedema	Test with vibration, for example Vortex mixer[4]	None
	Aquagenic urticaria	Provocation test[4]	None
	Cholinergic urticaria	Provocation and threshold test[4]	None
	Contact urticaria	Provocation test[4]	None

Abbr.: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TPO, thyroid peroxidase; UV, ultraviolet
[1] depending on suspected cause
[2] Unless strongly suggested by patient history, for example, 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[25]
[5] For patients in specialist care

TABLE 6 The aims of the diagnostic workup in patients with CSU

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		
Comorbidity	For example, check for CIndU, autoimmunity, mental health		
Consequences	For example, 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		

Key: modified according to Metz et al. (2021)[26]
Abbr.: CSU, chronic spontaneous urticaria; CSUaiTI, type I autoimmune (autoallergic) CSU; CSUaiTIIb, type IIb autoimmune CSU; UCT, urticaria control test
[1] including review of the patient photo documentation
[2] differential blood count, CRP/ESR; IgG anti-TPO, total IgE for patients in specialist care

Confirmation of and exclusion of differential diagnoses

Wheals or angioedema also occur in patients with diseases other than CSU (Figure 1). 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. These may be indicated by wheals that persist over a period of more than 24 hours, and a familial history. 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 medical history (Figure 1) and supported by basic tests such as CRP and/or ESR, differential blood count. Further testing should be

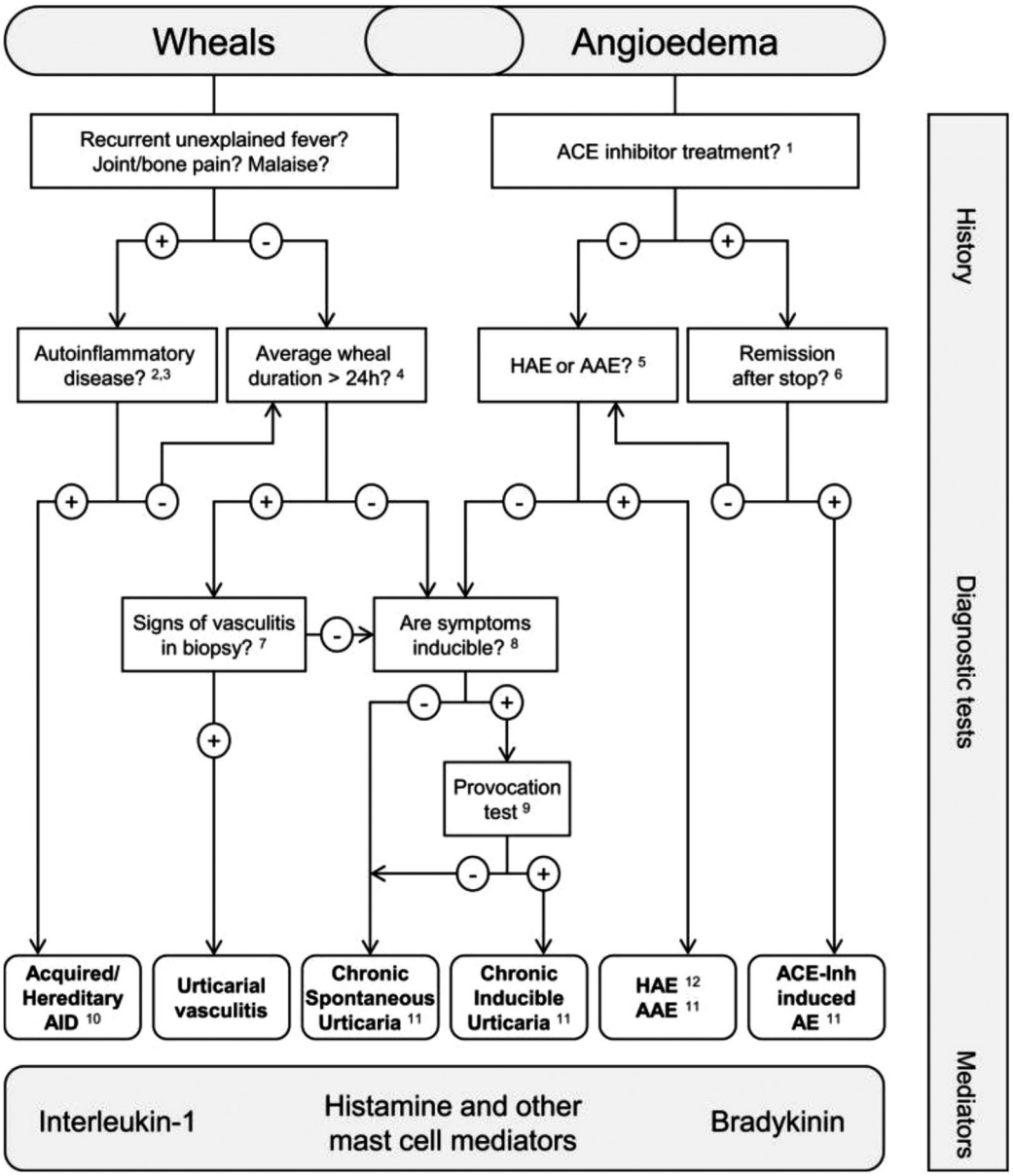


FIGURE 1 Diagnostic algorithm for patients presenting with wheals and/or angioedema for longer than 6 weeks. *Abbr.*: AAE: Acquired angioedema due to C1-inhibitor deficiency; ACE-Inh: angiotensin converting enzyme inhibitor; AE: angioedema; AID: Auto-inflammatory disease; HAE: Hereditary angioedema. 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 (for example, 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 45 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-Osulfotransferase 6) or unknown.

performed only as indicated by the results of the history, physical examination, and basic testing.

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, expert consensus

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

We recommend limited investigations at first. 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.	↑↑	Consensus, expert consensus
We recommend performing further diagnostic measures based on the patient history and examination, especially in patients with long-standing and/or uncontrolled disease.		

Should routine diagnostic measures be performed in inducible urticaria?

We recommend using provocation testing to diagnose chronic inducible urticaria.	↑↑	Strong consensus, expert consensus
We recommend using provocation threshold measurements and the urticaria control test (UCT) to measure disease activity and control in patients with chronic inducible urticaria, respectively.		

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.[4] 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 to 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 advised against due to limited benefits in terms of public health.

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.

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. Non-steroidal anti-inflammatory drugs (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 certain 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; 3–4 weeks are usually recommended. Importantly, diagnostic diets should not delay effective treatment.[27]

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.

Identification of comorbidities and consequences of CSU

In CSU, the most common comorbidities are chronic inducible urticaria (CIndU), autoimmune diseases, and allergies. Mental disorders, that is, 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.

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. Concomitant CIndU, high disease activity, elevated CRP, and/or the presence of angioedema, for example, point to long duration of CSU and poor response to antihistamine treatment

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 questionnaires (PROMs, patient-reported outcome measures) such as the urticaria activity score (UAS, and the weekly urticaria activity score, that is, UAS7, calculated from it), the angioedema activity score (AAS), the chronic urticaria quality of life questionnaire (CU-Q2oL, developed specifically for CSU), the angioedema quality of life questionnaire (AE-QoL), the urticaria control test (UCT), and the angioedema control test (AECT) should be used for this purpose. These questionnaires 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 7), a unified and simple scoring system that was proposed in the last version of the guideline and has been validated.[28,29] 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, that is, 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 7).[30] CSU patients who experience wheals and angioedema should use the UAS7 and the AAS in combination.

In addition to disease activity, it is important to assess the impact of disease on quality of life (QoL) 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).[31,32]

The UCT is a simple four-item tool with a clearly defined cutoff for patients with "well-controlled" vs. "poorly controlled" disease, and it is thus suited for the management of patients in routine clinical practice. Its recall period is 4 weeks. A 7 days recall period UCT version is also available (UCT7). The UCT cutoff 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.[33] Like the UCT, the AECT is a retrospective PROM. Two versions exist, one with a 4-week recall period and one with a 3-month recall period. The AECT consists, like the UCT, of only four questions. Its cutoff 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, expert consensus

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/or of the angioedema activity score, AAS, for assessing disease activity in patients with chronic spontaneous urticaria.	↑↑	Strong consensus, expert consensus

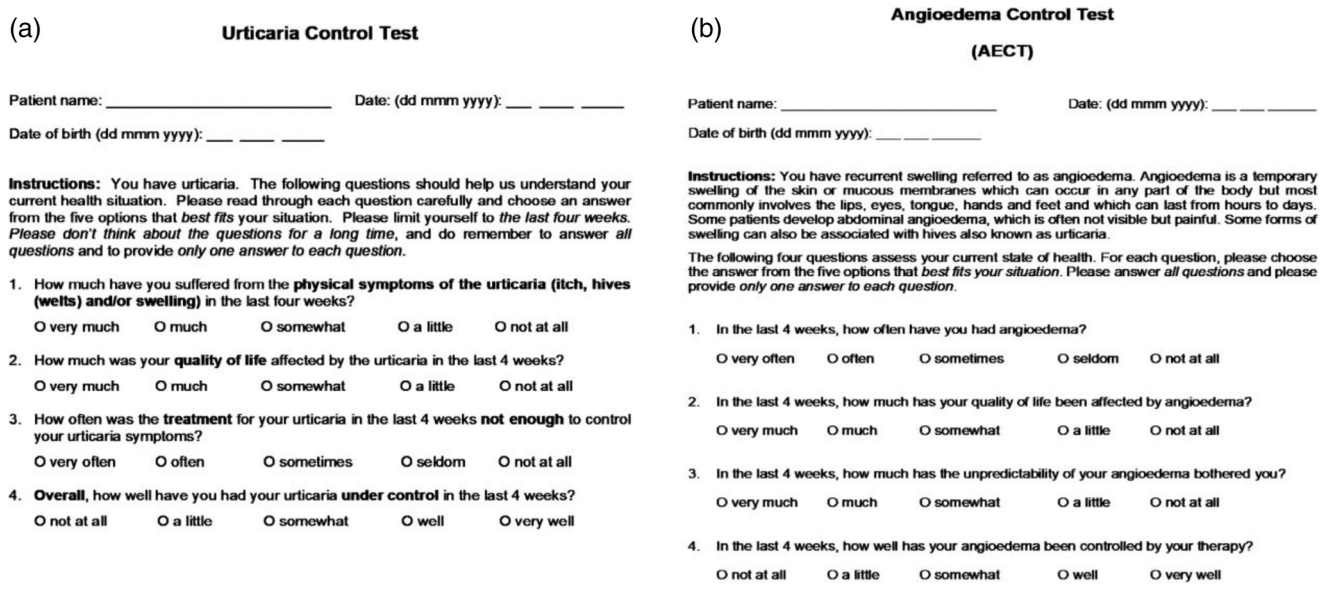
Which instruments should be used to assess and monitor quality of life impairment in chronic spontaneous urticaria patients?

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, expert consensus

TABLE 7 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 h?	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) (eg, 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 the score (0–3 for wheals +0–3 for pruritis) for each day is summarized over one week (7 days) for a maximum of 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: GA^{2}LEN; copyright for AAS (UK version): MOXIE GmbH (www.moxie-gmbh.de).



(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 The urticaria control test (UCT) (a) and the angioedema control test (AECT) (b). Copyright for both tools: MOXIE GmbH, Berlin, Germany (www.moxie-gmbh.de)

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, expert consensus

The diagnostic workup in CIndU

In patients with CIndU, the routine diagnostic workup should follow the consensus recommendations on the definition, diagnostic testing, and management of CIndUs.[25] Diagnostics in CIndU aim to exclude differential diagnoses, to identify the subtype of CIndU, and to determine

trigger thresholds.[25] The latter is important as it allows for assessing disease activity and response to treatment.

For most CIndU subtypes, validated tools for provocation testing are available.[25] Examples include cold and heat urticaria, where a Peltier element-based provocation device (Temp*Test*®) is available,[34] symptomatic dermographism for which dermographometers (Dermographic Tester®, FricTest®) have been developed,[35,36] and delayed pressure urticaria (Dermographic Tester®). In cholinergic urticaria, a graded provocation test with office-based methods, for example pulse-controlled ergometry, is available.[37,38] This can be used in day-to-day clinical practice without the need for a specialized center. Patients with contact urticaria or aquagenic urticaria should be assessed by appropriate cutaneous provocation tests.[25]

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 or are being developed for some CIndUs.[38,39]

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.[40–45]

The diagnostic workup 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.[46] If possible, that is, 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 currently available.

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 (insofar as this is possible in terms of age-related cooperation).

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