

SECTION 2

An individualized diagnostic approach based on guidelines for chronic urticaria (CU)

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Abstract

Chronic urticaria (CU), defined as the spontaneous or inducible appearance of hives, angioedema or both for 6 weeks or more, presents with a number of subtypes which all substantially impair patients' quality of life (QoL). International urticaria guidelines give clear recommendations on workup and treatment but the occurrence of CU with multiple causes and triggers (sometimes with more than one subtype occurring in a single patient) presents challenges for an individualized assessment by physicians. This review summarizes recent guidance on the classification, diagnosis and assessment of CU subtypes and discusses how currently available patient assessment tools and laboratory tests can be used in clinical practice as part of an individualized patient management plan.

Conflicts of interest

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Presentation and classification of chronic urticaria

Urticaria is one of the most common skin conditions, affecting as many as one in four individuals around the world during their lifetime.¹ It is characterized by the sudden appearance of hives (wheals), angioedema, or both.² Typical hives (Fig. 1a) have three features: (i) a central swelling of variable size surrounded by reflex erythema; (ii) itching that may be intense or, in some cases, a burning sensation; (iii) resolution within a few hours and usually within 24 h.² Angioedema (Fig. 1b) most frequently occurs beneath mucous membranes but may be anywhere on the integument. It is characterized by a sudden, pronounced swelling of the lower dermis and subcutis with a sensation of pain rather than itching. In contrast to hives, angioedema swellings can take as long as 72 h to resolve.²

The symptoms of urticaria are primarily mast cell-mediated.^{2,3} Many specific factors that induce mast cell activation

have been described in chronic spontaneous urticaria (CSU) (also called chronic idiopathic urticaria [CIU]), including autoimmune mechanisms in up to 50% of cases,^{4,5} although the cause quite commonly remains unknown (idiopathic). Once activated, the stimulated mast cells release inflammatory mediators such as histamine, which stimulate the sensory nerves, leading to itchiness and promote vasodilation with plasma extravasation.^{2,6} Platelet activating factor, together with other newly synthesized or preformed mast cell mediators, promotes the dermal lesion skin infiltration of other immune cells, including neutrophils, eosinophils, T-lymphocytes and basophils.^{3,7–10}

The European Academy for Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA²LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) 2013 guideline classification of urticaria is based on the duration of symptoms, frequency and cause (Fig. 2).² Acute urticaria is defined as being of less than 6 weeks'



Figure 1 Clinical appearance of the characteristic symptoms of urticaria. (a) hives; (b) angioedema affecting the mouth (case provided by E. Toubi).

duration and accounts for the majority of cases (10–20% lifetime prevalence).^{2,11} These acute reactions can be triggered by a specific food or drug, and in children are often associated with infection.^{2,12,13} Chronic urticaria (CU) is defined as daily or almost daily urticaria for 6 weeks or more. It is called chronic spontaneous urticaria (CSU; previously referred to as idiopathic or ordinary) if swellings are spontaneous, or chronic inducible urticaria (CINDU) where a physical or other eliciting trigger can be identified.² CSU may be secondary to functional autoantibodies or infection but the cause of CINDU remains unknown, except in the case of contact urticaria, which may be allergic or non-immunological. CSU is the predominant form of CU, accounting for >75% of cases and affecting 0.5–1.0% of the population.¹ In some cases, patients present with more than one subtype of urticaria (e.g. CSU with an inducible urticaria) or with overlapping subtypes of CINDU,¹ which can make diagnosis challenging.

The impact of CU on patients' quality of life (QoL) is often underestimated, but is in fact similar or greater than that of other chronic skin conditions that cause severe impairment, such as psoriasis and atopic dermatitis.¹⁴ The symptoms of CU have a substantial adverse impact on patients' daily living/leisure activities, sleep, mobility, mental status, social functioning and self-perception; loss of sleep in particular is a major problem for

patients.^{15,16} Symptoms have been reported to reduce productivity at school or work by 25–30%.¹⁷ Swelling and itching are reported by patients to be the worst aspects of the condition.¹⁶ The presence of angioedema or psychiatric comorbidities, such as anxiety and depression, further impair patients' QoL.^{18,19}

Chronic spontaneous urticaria

Chronic spontaneous urticaria presents with hives alone in approximately 50% of cases and with concurrent angioedema in approximately 40% of cases.¹ A minority of patients (~10–15%) will present with angioedema alone.¹ Hereditary angioedema and drug-induced angioedema should be considered in the differential diagnosis,^{20,21} particularly as some forms of drug-induced angioedema can become life-threatening if the upper airways are affected.^{21,22}

In the majority of cases, CSU usually resolves within 1–5 years,¹ although approximately 10–20% of cases can take up to 5–10 years to resolve.^{1,23,24} Rare cases lasting up to 50 years have also been reported.¹ Several indicators of disease duration have been reported that may be useful to identify subtypes of CSU with a different clinical course. For example a significant association between disease severity at diagnosis and duration has been demonstrated.²⁵ In one 5-year study of 145 patients with CSU, all cases of mild severity resolved within 2 years ($P < 0.0001$).²⁵ In contrast, only 41% of moderate to severe CSU cases resolved within 2 years and 30% of patients were still experiencing symptoms at 5 years.²⁵ Other markers of disease severity that have been associated with longer disease duration include the occurrence of angioedema, in combination with hives or alone, concurrent CINDU with a physical cause and a positive autologous serum skin test (ASST).^{1,25–27}

Chronic inducible urticaria

Chronic inducible urticarias may be elicited by external physical triggers, such as temperature (cold or heat contact urticaria), sustained local pressure (delayed pressure urticaria, symptomatic dermographism), vibration (vibratory urticaria) and sunlight (solar urticaria) (Fig. 2).²⁸ They may also be triggered by an increased core body temperature (cholinergic urticaria) or, rarely, by water contact (aquagenic urticaria).²⁸ Some cases of contact urticaria may be chronic if the association between triggering factor and urticaria is not recognized, although the eliciting cause is usually obvious at presentation and exposure to the trigger can be avoided. Patients can present with overlapping physical urticarias, or may have summation physical urticaria where more than one stimulus is required simultaneously to elicit a rash.

Diagnostic procedures and assessments

The key goals of the recent diagnosis and management guidelines for CU are to confirm CSU or CINDU and exclude differential diagnoses, identify a cause where appropriate, and measure disease activity, impact and control.²

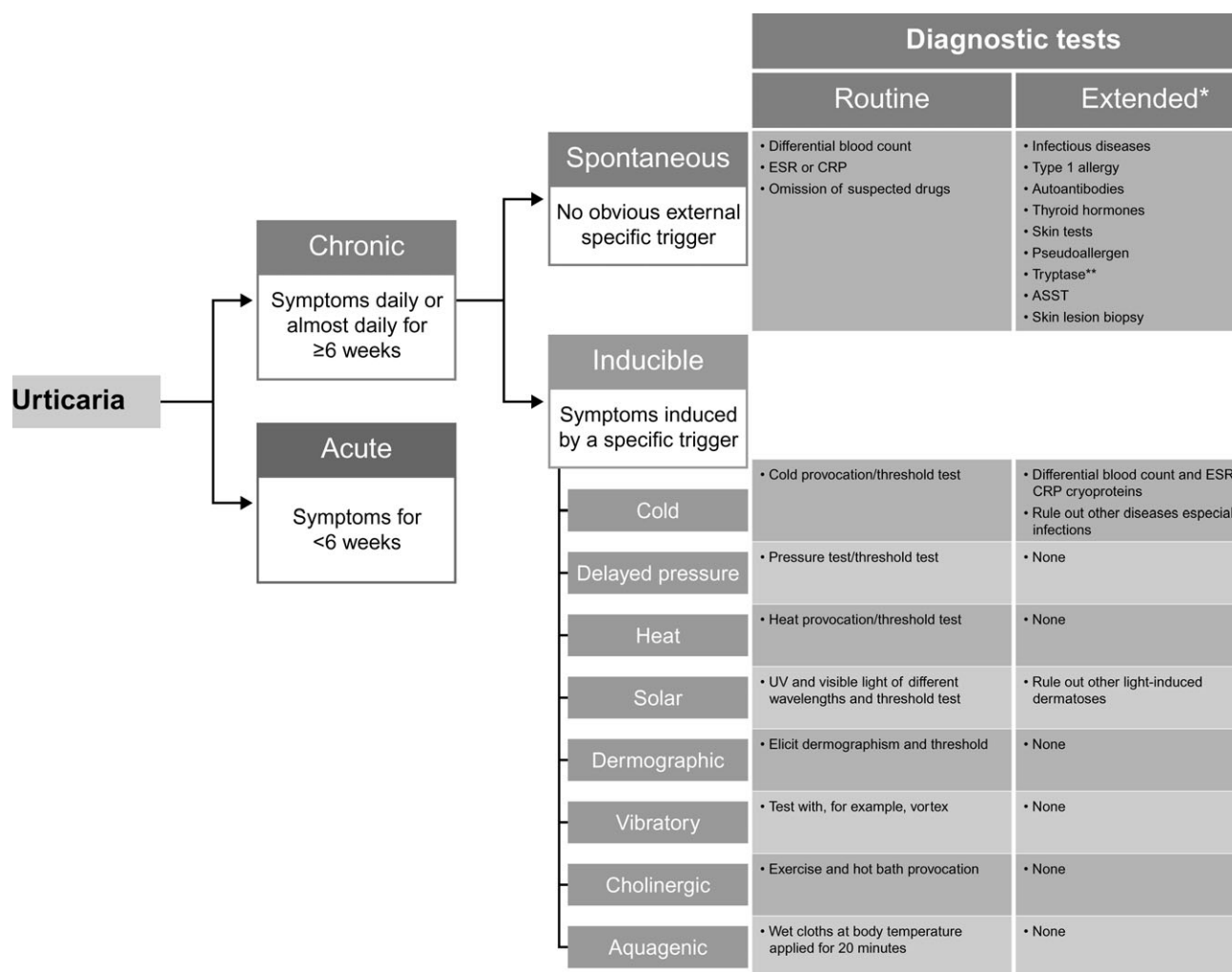


Figure 2 EAACI/GA²LEN/EDF/WAO 2013 guideline classification of urticaria and recommended diagnostic tests for urticaria subtypes.²
 *Depending on suspected cause. **As indication of severe systemic disease. ASST, autologous serum skin test; CRP, C-reactive protein; EAACI, European Academy for Allergy and Clinical Immunology; EDF, European Dermatology Forum; ESR, erythrocyte sedimentation rate; GA²LEN, Global Allergy and Asthma European Network; WAO, World Allergy Organization. Reproduced from Zuberbier *et al.* Allergy 2014;69(7):868–87. Copyright © 2015 Wiley, with permission.

Diagnosis of CU

The EAACI/GA²LEN/EDF/WAO guidelines recommend the use of a diagnostic algorithm (Fig. 3)² to distinguish CU from other conditions that can present with hives or angioedema, or to distinguish between urticaria subtypes. Causes of hives that are important to exclude at diagnosis include urticaria vasculitis and auto-inflammatory disorders.²⁹ These can usually be distinguished by the clinical presentation of the hives, systemic involvement or by blood analysis. An important first step therefore in the diagnosis of CU is to identify the hive as the elemental lesion of the rash. Then diagnosis of urticaria is based on patient history, which should address factors such as duration

and appearance of hives, symptoms and use of medication. For those patients also experiencing fever or joint pain, an auto-inflammatory condition may be suspected, or urticarial vasculitis. In the case of hives that do not resolve within 24 h, a skin biopsy should be taken, as histology may indicate urticarial vasculitis. Physical examination might include provocation tests for CINDU for some patients if the history indicates specific triggers.²

For patients with suspected CSU, EAACI/GA²LEN/EDF/WAO urticaria guidelines recommend that routine assessment should focus on patient history and clinical and physical signs, avoiding extensive diagnostic tests for all possible causes as these

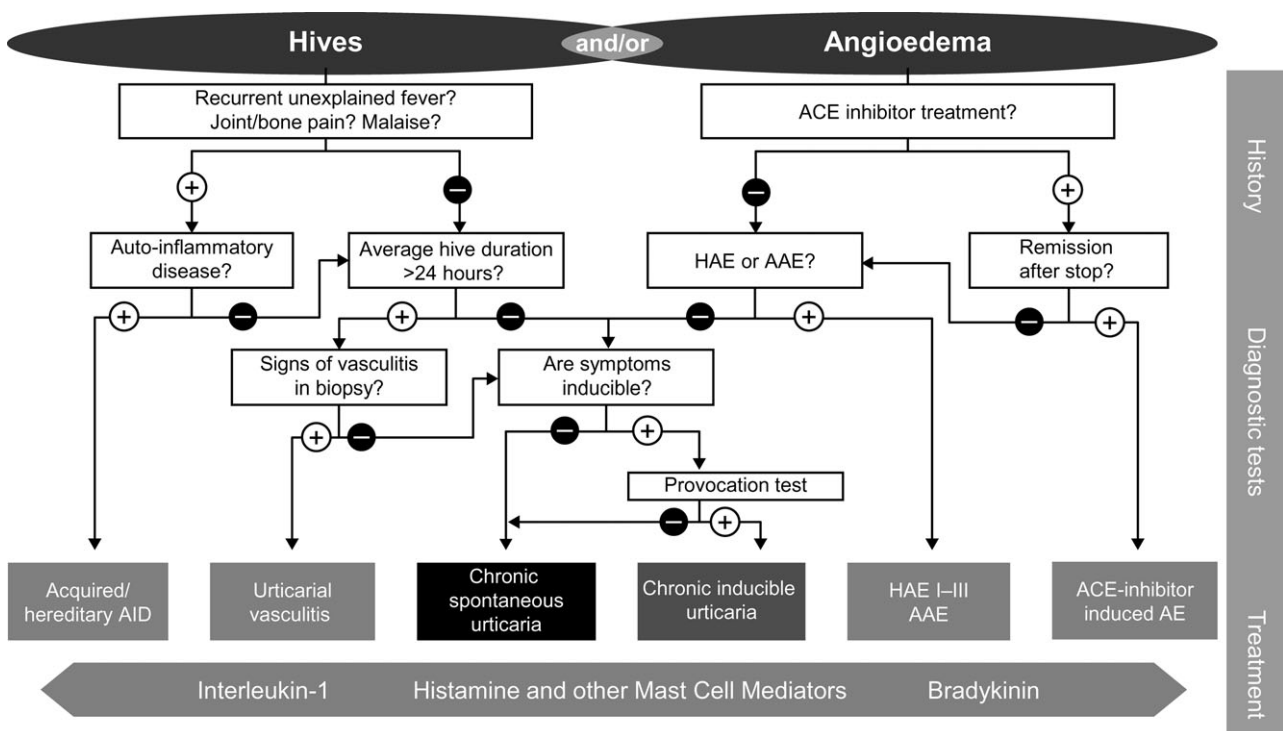


Figure 3 EAACI/GA²LEN/EDF/WAO 2013 guideline-recommended diagnosis algorithm for urticaria.² ACE, angiotensin converting enzyme; AAE, acquired angioedema due to C1 inhibitor deficiency; AE, angioedema; AID, auto-inflammatory disease; EAACI, European Academy for Allergy and Clinical Immunology; EDF, European Dermatology Forum; GA²LEN, Global Allergy and Asthma European Network; HAE, hereditary angioedema; WAO, World Allergy Organization. Reproduced from Zuberbier *et al.* Allergy 2014;69(7):868–87. Copyright © 2015 Wiley, with permission.

are unnecessary and costly.² Routine diagnostic measures should be limited to a differential blood count, measurement of erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels and omission of any drugs suspected of causing a reaction (Fig. 2).² These measures will rule out any serious underlying systemic disease. Use of extended diagnostic testing to identify underlying causes and exclude other diagnoses is recommended only for patients with severe or long-standing CSU. Extended diagnostic tests might include tests for infection (e.g. *Helicobacter pylori*), skin prick tests for allergy, autoantibodies, autologous serum skin tests and skin biopsy (Fig. 2).²

For patients with a diagnosis of CINDU, it is recommended that routine diagnostic tests are limited to determining the threshold of eliciting factors (Fig. 2).² These will be discussed in more detail below.

Laboratory diagnostic tests

The EAACI/GA²LEN/EDF/WAO urticaria guidelines recommend extended diagnostic testing if the patient's history is relevant (Fig. 2).² CSU caused by autoimmunity is being recognized with increasing frequency³⁰ and is thought to account for approximately 45% of cases of CSU.⁵ In CSU suspected to be

caused by autoimmunity, ASST can confirm that autologous serum injection can induce autoreactivity.³¹ However, this test has a sensitivity and specificity of only 80% for a positive *in vitro* basophil histamine release assay and is not a specific test of functional autoantibodies. The clinical significance of a positive autologous plasma skin test (APST) has been questioned.^{32,33} In up to 50% of patients with CSU caused by autoimmunity, circulating functional autoantibodies against immunoglobulin E (IgE) or against the high-affinity IgE receptor can be detected.³⁴ In 2013, the EAACI Taskforce highlighted the need for defined criteria for diagnosis of autoimmune CSU and proposed that these criteria should include confirmation of functional activity of autoantibodies (by the basophil histamine release assay) and specificity (by immunoassay).^{30,34} An assay using the marker CD63 to detect activation of healthy donor basophils by CSU sera has also been described for autoimmune CSU and correlates with a positive ASST result and disease activity.³⁵ Such *in vitro* tests, however, need to be performed in specialized research laboratories which are only available in some countries. Hence, these tests are currently of limited use for everyday clinical practice. Other immunoassays are also being investigated. Serum testing for IgE directed against autoantigens may be helpful to

understand the pathological mechanisms involved in CSU and aid identification of patients who are candidates for immunomodulatory therapy. For example a study reported that approximately 50% of patients with CSU express IgE against thyroid peroxidase and this has been hypothesized to cause autoallergic mast cell activation.³⁶

Biomarkers of disease activity and response to treatment that can be applied in practice would be of value for the management of CSU patients. Recent studies have reported the use of blood D-dimer and substance P as potential markers of disease activity and response to treatment.^{37,38} However, additional scientific and clinical research is required to develop informative biomarkers for CSU.

Tools for diagnosis and assessment of CSU

In order to develop an individualized management programme for patients with CSU, several aspects of the condition need to be assessed to provide more information on the prognosis and help guide treatment and assess response. Assessments should include disease duration and severity, disease control, QoL and comorbidities. Many of the instruments widely used in the diagnosis and assessment of CU are completed by both patient and physician. Patient-reported outcome (PRO) data are particularly important for assessing disease status in the management of CU due to the substantial impact of the symptoms on many aspects of patients' lives.^{15,16} The episodic and unpredictable nature of urticaria also means that physicians are reliant on information from the patient on their disease activity and impact between clinic visits.

Instruments for assessing disease activity

The tool recommended by the EAACI/GA²LEN/EDF/WAO urticaria guidelines for measuring disease activity and response to treatment in clinical practice is the Urticaria Activity Score (UAS; Table 1), a validated composite score of the Itch Severity Score (ISS) and number of hives score.^{2,39} It is recommended

that disease activity is documented using the UAS over a period of 7 days, giving a total weekly Urticaria Activity Score (UAS7) of 0–42. The UAS7 is completed by the patient and has been used in clinical trials. The use of UAS7 by patients to evaluate their hives and pruritus daily for 7 days provides semi-quantitative information on disease activity between clinic visits and captures changes in intensity and possible triggers. In a phase III trial of omalizumab in CSU,⁴⁰ patients were categorized using UAS7, according to the severity of their disease, as either itch/hive-free (0), well controlled (1–6), mild (7–15), moderate (16–27), or severe (28–42). UAS7 scores were also found to correlate with patient QoL, as measured using the Dermatology Life Quality Index (DLQI).⁴⁰ The utility of the UAS7 as an indicator of QoL, however, requires further validation in studies using the DLQI and other PRO instruments. The UAS7 is limited in that it can only be recorded prospectively. In addition, it does not assess angioedema and is not suitable for use in CINDU.

The Angioedema Activity Score (AAS) is a new instrument that can be used to assess angioedema activity, but does not provide a composite score of angioedema, hives and itch.⁴¹ It includes questions on the occurrence and severity of angioedema as well as its impact on patients' daily activities and appearance. The questionnaire is completed by the patient on a weekly basis, over a 4 week period, and can be used to categorize disease severity as mild (~25 points), moderate (~60 points) or severe (~80 points). The original version of the AAS has now been translated from German into several languages, including English, French, Italian, Japanese, Spanish and Swedish.

Disease control

The Urticaria Control Test (UCT)⁴² is a validated instrument that can be used by patients (with either CSU or CINDU) and physicians to assess disease control over the past 4 weeks.⁴² Four questions address the control of signs and symptoms of the disease, QoL impairment, efficacy of treatment, and overall disease control. The answer to each question is rated from 0 (very much) to 4 (not at all) and a total score is calculated, where the highest possible score of 16 indicates complete control. A score of ≤11 indicates poor disease control.⁴² The UCT can be used for *ad hoc* assessment.

Quality of Life (QoL) Instruments

Validated and reliable PRO instruments for assessing QoL impairment are available for patients with urticaria and angioedema. The EAACI/GA²LEN/EDF/WAO urticaria guidelines recommend the use of the validated Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) and the AngioEdema (AE-QoL) instrument (for patients with angioedema but no hives) to assess and monitor QoL impairment and disease activity in CSU.²

The CU-Q2oL questionnaire was the first QoL instrument to be developed that is specific for CU, and assesses physical,

Table 1 Urticaria Activity Score (UAS) to assess disease severity.² Reproduced from Zuberbier *et al.* Allergy 2014;69(7):868–87.² Copyright © 2015 Wiley, with permission.

Score	Hives (wheals)	Score	Itch Severity Score (ISS)
0	None	0	None
1	Mild (<20 hives/24 h)	1	Mild (present, but not annoying or troublesome)
2	Moderate (20–50 hives/24 h)	2	Moderate (troublesome, but does not interfere with normal daily activity or sleep)
3	Intense (50 hives/24 h or large confluent areas of hives)	3	Intense (severe itch, which is sufficiently troublesome to interfere with normal daily activity or sleep)

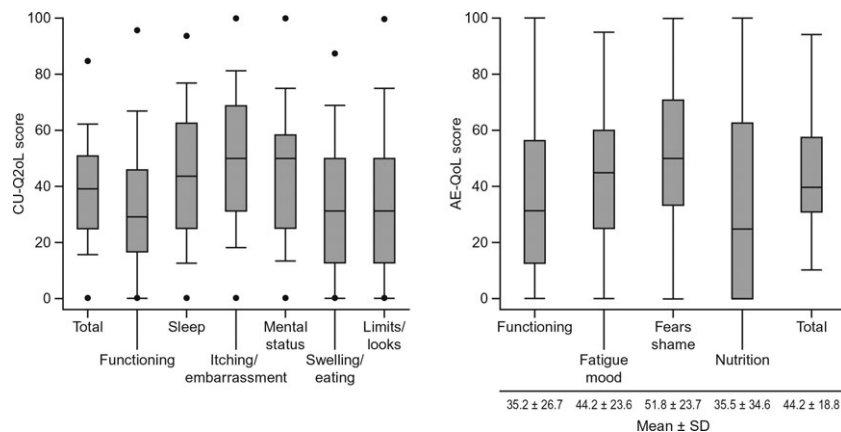


Figure 4 Quality of life impairment assessed using (a) the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) and (b) the Angioedema Quality of Life Questionnaire (AE-QoL).^{22,47} Box-and-whisker plot showing the distribution of a) CU-Q2oL and b) AE-QoL scores. The higher the scores, the greater the impairment to quality of life. The middle line of each box represents the median score. The ends of each box represent the 25th and 75th percentiles. The whisker ends represent the 10th and 90th percentiles in (a) and minimum and maximum values in (b). Minimum and maximum scores are represented by dots in (a). Mean scores $\pm$ standard deviation (SD) are shown for AE-QoL (b). Reproduced from Weller *et al.* Allergy 2012;67(10):1289–98.²² Reproduced from Mlynek *et al.* Allergy 2009;64(6):927–36.⁴⁷ Copyright © 2015 Wiley, with permission.

emotional, social and practical aspects of the condition over a 2-week period.⁴³ The questionnaire includes 23 items, within six domains: functioning; sleep; itching/embarrassment/mental status; swelling/eating; limits and looks (Fig. 4).⁴³ Patients rate the individual items within each domain from 0 (never) to 4 (very often) and a total CU-Q2oL score (0–100) is calculated based on the sum of all completed items/total possible score of all completed items $\times$ 100.⁴³ Scores for each individual domain can also be calculated. The CU-Q2oL questionnaire was originally developed for use in Italy⁴³ but has now been translated and validated for use in Brazil, Bulgaria, Germany, Greece, Poland, Portugal, Spain and Turkey.^{44–48}

The AE-QoL questionnaire assesses symptom-specific QoL impairment over a 4-week period in patients with recurrent angioedema.²² The questionnaire, developed in Germany, has now been translated for use in different countries (e.g. Canada, France, Greece, Japan, Italy, Russia, Spain, Sweden and the USA). Four dimensions are examined: functioning; fatigue/mood; fears/shame and nutrition (Fig. 4). Patients score individual items within each dimension from 0 (never) to 4 (very often) and a total AE-QoL score (0–100) is calculated based on the sum of all completed items/total possible score of all completed items $\times$ 100.²² Scores for each individual dimension can also be calculated.

Comorbidities

Chronic spontaneous urticaria is associated with a number of comorbidities (e.g. depression/anxiety, autoimmune diseases, thyroid dysfunction, metabolic diseases, atopic disorders or *H. pylori* gastritis).^{2,49,50} These need to be considered in the diagnosis and

management of patients with CSU, as conditions such as depression may have further impact on QoL.¹⁹ Similarly, symptoms of CSU such as itching can influence the severity of associated depressive symptoms.^{1,50} The extended diagnostic procedures recommended in the EAACI/GA²LEN/EDF/WAO urticaria guidelines include a number of tests for patients with a relevant history. These include tests for infection (e.g. *H. pylori*, *Streptococcus spp.*, *Staphylococcus sp.*, *bowel parasites*), type 1 allergy (IgE, skin prick test), functional autoantibodies, thyroid hormones and non-organ-specific autoantibodies (e.g. anti-nuclear antibodies [ANA]), skin tests including physical tests to rule out inducible additional urticaria, assessment of autoreactivity and a pseudoallergen-free diet.

Specific tools for diagnosis and assessment of CINDU

Diagnosis of CINDU should be based on confirmation of CINDU and exclusion of differential diagnoses, identification of triggers, confirmation by provocation/challenge and assessment of thresholds (Fig. 2).² An important aspect of the history of a patient with CINDU is the duration of hives, as in most cases of CINDU hives last for ≤ 1 h, with the exception of contact urticaria (2 h) and delayed pressure urticaria (24 h).⁵¹ The clinical presentation can also help to distinguish between the subtypes of CINDUs (Fig. 5). Provocation and threshold testing methods for physical and cholinergic urticarias generally provide results within minutes and have been recommended by the EAACI/GA²LEN/EDF/UNEV (urticaria network e.V.).²⁸ H₁-antihistamines should be withdrawn prior to testing as this may affect results.²⁸ There are no published disease activity assessment tools specifically for CINDU, although the UCT may be used.⁴² In

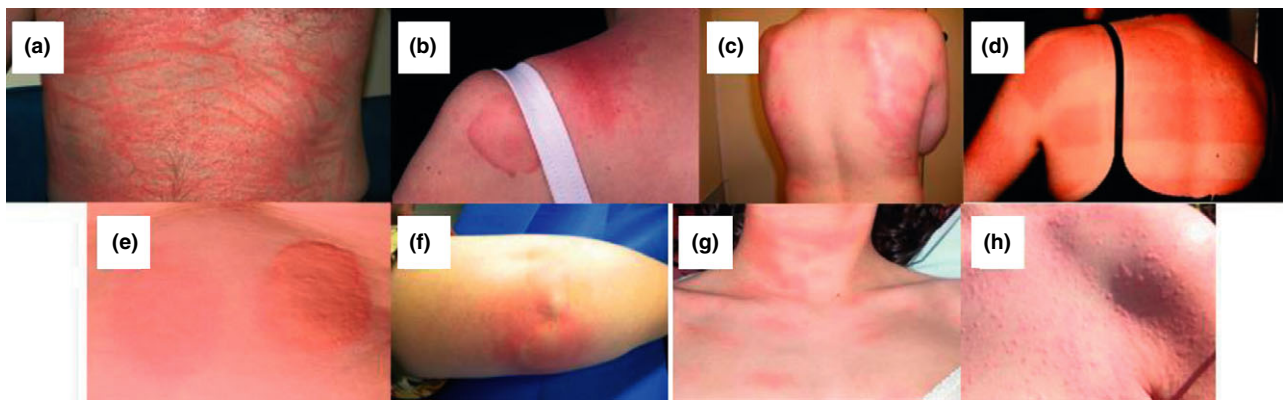


Figure 5 Clinical presentation of various CINDUs: (a) symptomatic dermographism; (b) delayed pressure urticaria; (c) cold contact urticaria; (d) solar urticaria; (e) heat contact urticaria; (f) vibratory urticaria; (g) aquagenic urticaria; (h) cholinergic urticaria (case provided by C. Grattan).

contrast to CSU, there are no specific QoL instruments that are appropriate for use by patients with physical or cholinergic urticarias. The Dermatology Life Quality Index (DLQI),⁴³ is useful, however.

Provocation and threshold testing for physical urticarias

Symptomatic dermographism is characterized by hives and itching triggered by rubbing and scratching (Fig. 5a). It is the most common form of physical urticaria.⁵² Provocation and threshold testing are usually performed on the upper back or volar forearm. For provocation testing, a blunt, smooth instrument can be used to stroke the skin. Several instruments are available that can also be used to determine thresholds. A calibrated spring-loaded dermatographometer is a useful instrument as it can be used to apply different pressures (20–60 g/mm²), thus enabling simultaneous threshold testing.⁵² An alternative method is the Fric Test[®], which consists of six tips stroked over the skin to determine provocation thresholds.⁵³

Delayed pressure urticaria is caused by sustained pressure (e.g. from seatbelts, clothing, bags, etc.) and can present alongside CSU (Fig. 5b).²⁸ Traditionally, delayed pressure urticaria has been diagnosed and assessed by application of metal rods of different weight to the skin of the upper back, shoulder, volar forearm or thigh. The rods should be applied to the skin for 15 min, which can be painful for the patient, and a result may not be evident for up to 6 h.²⁸ A simpler and more convenient method is the use of a dermatographometer which can be adjusted to apply different amounts of pressure (100 g/mm²) and requires only 70 s for testing.

Cold contact urticaria can be triggered by exposure to cold temperatures and subsequent rewarming of the skin (Fig. 5c).⁵⁴ This can be confirmed simply by testing whether application of a melting ice cube in thin polythene for 5 min to the skin of the patient's forearm elicits a hive response. The ice should be

melting to avoid skin damage at temperatures <0°C and should be placed in a plastic bag to avoid confusion with aquagenic urticaria (Fig. 5g).²⁸ Cold contact stimulation tests using testing kits (e.g. TempTest[®]) can be used to determine the critical temperature thresholds for cold contact urticaria or the more rare heat-contact urticaria (Fig. 5e).⁵⁵ In clinical trials, use of TempTest[®] has been shown to provide a useful measure of changes in critical temperature thresholds in response to antihistamine therapy.⁵⁶

Solar urticaria is triggered by exposure to ultraviolet (UV) light (Fig. 5d). It can be confirmed by dermatologists in provocation tests using a solar simulator to apply UVA (up to 6 J/cm²) and UVB (up to 0.06 J/cm²) or a projector to apply visible light (to exclude other causes) to patches of skin on the buttocks.²⁸ An urticarial response is usually visible within 10 min. Specialist reference centres can provide more sophisticated threshold testing to identify the specific dose and wavelength of light leading to a reaction.

Vibratory angioedema, although rare, can be diagnosed with use of a laboratory vortex mixer at 1000 rpm for 10 min on the volar forearm (Fig. 5f).²⁸

Provocation and threshold testing for cholinergic urticaria

Cholinergic urticaria can be induced by an increase in core body temperature through exercise or by passive warming (e.g. through bathing in hot water up to 42°C; Fig. 5h).²⁸ Provocation tests should include ergometric testing (e.g. use of an exercise machine or physical activity of any description to the point of sweating). If this test is positive, it should be followed by bathing at 42°C for 15 min to increase body temperature by ≥1°C.²⁸ A positive exercise test but negative hot bath test indicates exercise-induced urticaria. Recently, a novel standardized pulse-controlled ergometry test has been described for both provocation and threshold testing and assessment of disease severity.⁵⁷

Testing for contact urticaria

Contact urticaria can present as localized burning/itching at the point of contact through to anaphylaxis (previously called the contact urticaria syndrome).⁵⁸ It can be classified as immunological (IgE- and histamine-mediated, rapid onset) or non-immunological (non IgE- or histamine-mediated, slow onset).⁵⁸ These two forms may be associated with different causes. Open or closed patch skin testing can be used to test for contact urticaria.² Skin prick tests using histamine as positive control or extracts from suspected allergens can confirm IgE-mediated cases.⁵⁹ In-use challenge skin prick testing with potential triggers, (e.g. fruits, latex gloves, etc.) applied directly to the skin can be very useful. Any provocation test should be conducted with caution and facilities for emergency treatment during provocation should be available.

Laboratory diagnostic tests

In terms of laboratory tests, none are specifically recommended for CINDU, with the exception of blood count, ESR and CRP for cold urticaria to screen for familial cold autoinflammatory syndrome, and cryoglobulins for secondary cold contact urticaria, depending on patient history (Fig. 2).² Further research is required to identify molecular and immunological markers of the various subtypes. While this subtype of CU is also thought to be mediated by mast cells and histamine, the pathological mechanisms involved are likely to differ from CSU and other inflammatory mediators and autoantibodies have been implicated.⁶⁰

Summary and conclusions

Chronic urticaria is a heterogeneous condition, characterized by pruritic hives with or without angioedema, and has a substantial negative impact on many aspects of patients' lives. CU can be classified into a number of subtypes which differ in duration and cause. The most frequently occurring form, CSU, may be associated with circulating autoantibodies, however, for approximately 50% of patients there is no identifiable cause. CINDUs, associated with physical or other triggers, are less common than but can often present alongside CSU. Early diagnosis of CU and use of assessments appropriate for the individual patient are important for monitoring disease activity and guiding treatment. The 2013 update to the EAACI/GA²LEN/EDF/WAO guidelines highlights the importance of patient history for diagnosis and assessment of disease severity and recommends limited laboratory testing to exclude underlying systemic disease. Use of extended diagnostic testing to explore possible causes is also warranted in some patients and should be used in cases of CINDU to identify thresholds of eliciting factors. A number of validated PRO-based instruments have now been developed specifically for CU and should be used as part of an individual patient management programme to assess disease activity and impact. While there is some evidence that autoantibodies and other biomarkers may be

of use to monitor disease activity, there is a need for further research to phenotype CU subtypes and identify markers that can be used in routine clinical practice.

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References

- Maurer M, Weller K, Bindslev-Jensen C *et al.* Unmet clinical needs in chronic spontaneous urticaria. A GA²LEN task force report. *Allergy* 2011; **66**: 317–330.
- Zuberbier T, Aberer W, Asero R *et al.* The EAACI/GA²LEN/EDF/WAO Guideline for the definition, classification, diagnosis and management of Urticaria. The 2013 revision and update. *Allergy* 2014; **69**: 868–887.
- Elias J, Boss E, Kaplan AP. Studies of the cellular infiltrate of chronic idiopathic urticaria: prominence of T-lymphocytes, monocytes, and mast cells. *J Allergy Clin Immunol* 1986; **78**: 914–918.
- Greaves M. Chronic urticaria. *J Allergy Clin Immunol* 2000; **105**: 664–672.
- Kaplan AP, Greaves M. Pathogenesis of chronic urticaria. *Clin Exp Allergy* 2009; **39**: 777–787.
- Jensen BM, Falkencrone S, Skov PS. Measuring histamine and cytokine release from basophils and mast cells. *Methods Mol Biol* 2014; **1192**: 135–145.
- Ito Y, Satoh T, Takayama K, Miyagishi C, Walls AF, Yokozeki H. Basophil recruitment and activation in inflammatory skin diseases. *Allergy* 2011; **66**: 1107–1113.
- Natbony SF, Phillips ME, Elias JM, Godfrey HP, Kaplan AP. Histologic studies of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1983; **71**: 177–183.
- Sabroe RA, Poon E, Orchard GE *et al.* Cutaneous inflammatory cell infiltrate in chronic idiopathic urticaria: comparison of patients with and without anti-FcεRI or anti-IgE autoantibodies. *J Allergy Clin Immunol* 1999; **103**: 484–493.
- Ying S, Kikuchi Y, Meng Q, Kay AB, Kaplan AP. TH1/TH2 cytokines and inflammatory cells in skin biopsy specimens from patients with chronic idiopathic urticaria: comparison with the allergen-induced late-phase cutaneous reaction. *J Allergy Clin Immunol* 2002; **109**: 694–700.
- Swinny B. The atopic factor in urticaria. *South Med J* 1941; **34**: 855–858.
- Mortureux P, Leaute-Labreze C, Legrain-Lifermann V, Lamireau T, Sarlangue J, Taieb A. Acute urticaria in infancy and early childhood: a prospective study. *Arch Dermatol* 1998; **134**: 319–323.
- Sackesen C, Sekerel BE, Orhan F, Kocabas CN, Tuncer A, Adalioglu G. The etiology of different forms of urticaria in childhood. *Pediatr Dermatol* 2004; **21**: 102–108.
- Grob JJ, Revuz J, Ortonne JP, Auquier P, Lorette G. Comparative study of the impact of chronic urticaria, psoriasis and atopic dermatitis on the quality of life. *Br J Dermatol* 2005; **152**: 289–295.
- Kang MJ, Kim HS, Kim HO, Park YM. The impact of chronic idiopathic urticaria on quality-of-life in Korean patients. *Ann Dermatol* 2009; **21**: 226–229.
- O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. *Br J Dermatol* 1997; **136**: 197–201.
- Thompson AK, Finn AF, Schoenwetter WF. Effect of 60 mg twice-daily fexofenadine HCl on quality of life, work and classroom productivity, and regular activity in patients with chronic idiopathic urticaria. *J Am Acad Dermatol* 2000; **43**: 24–30.

- 18 Silveiras MR, Fortes MR, Miot HA. Quality of life in chronic urticaria: a survey at a public university outpatient clinic, Botucatu (Brazil). *Rev Assoc Med Bras* 2011; **57**: 577–582.
- 19 Staubach P, Onnen K, Vonend A *et al*. Autologous whole blood injections to patients with chronic urticaria and a positive autologous serum skin test: a placebo-controlled trial. *Dermatology* 2006; **212**: 150–159.
- 20 Bork K. An evidence based therapeutic approach to hereditary and acquired angioedema. *Curr Opin Allergy Clin Immunol* 2014; **14**: 354–362.
- 21 Loftus PA, Tan M, Patel G *et al*. Risk factors associated with severe and recurrent angioedema: an epidemic linked to ACE-inhibitors. *Laryngoscope* 2014; **124**: 2502–2507.
- 22 Weller K, Groffik A, Magerl M *et al*. Development and construct validation of the angioedema quality of life questionnaire. *Allergy* 2012; **67**: 1289–1298.
- 23 Beltrani VS. An overview of chronic urticaria. *Clin Rev Allergy Immunol* 2002; **23**: 147–169.
- 24 Champion RH, Roberts SO, Carpenter RG, Roger JH. Urticaria and angioedema. A review of 554 patients. *Br J Dermatol* 1969; **81**: 588–597.
- 25 Toubi E, Kessel A, Avshovich N *et al*. Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients. *Allergy* 2004; **59**: 869–873.
- 26 Kozel MM, Mekkes JR, Bossuyt PM, Bos JD. Natural course of physical and chronic urticaria and angioedema in 220 patients. *J Am Acad Dermatol* 2001; **45**: 387–391.
- 27 Staubach P, Eckhardt-Henn A, Dechene M *et al*. Quality of life in patients with chronic urticaria is differentially impaired and determined by psychiatric comorbidity. *Br J Dermatol* 2006; **154**: 294–298.
- 28 Magerl M, Borzova E, Giménez-Arnau A *et al*. The definition and diagnostic testing of physical and cholinergic urticarias - EAACI/GA²LEN/EDF/UNEV consensus panel recommendations. *Allergy* 2009; **64**: 1715–1721.
- 29 Jachiet M, Flageul B, Deroux A *et al*. The clinical spectrum and therapeutic management of hypocomplementemic urticarial vasculitis: data from a French nationwide study of fifty-seven patients. *Arthritis Rheumatol* 2015; **67**: 527–534.
- 30 Konstantinou GN, Asero R, Ferrer M *et al*. EAACI taskforce position paper: evidence for autoimmune urticaria and proposal for defining diagnostic criteria. *Allergy* 2013; **68**: 27–36.
- 31 Sabroe RA, Grattan CE, Francis DM, Barr RM, Kobza BA, Greaves MW. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol* 1999; **140**: 446–452.
- 32 Asero R, Tedeschi A, Cugno M. Is the autologous plasma skin test in patients with chronic urticaria really useless? *J Allergy Clin Immunol* 2009; **123**: 1417–1418.
- 33 Metz M, Giménez-Arnau A, Borzova E, Grattan CE, Magerl M, Maurer M. Frequency and clinical implications of skin autoreactivity to serum versus plasma in patients with chronic urticaria. *J Allergy Clin Immunol* 2009; **123**: 705–706.
- 34 Lee MF, Lin TM, Liu SW, Chen YH. A rapid method of detecting autoantibody against FcεpsilonRIα for chronic spontaneous urticaria. *PLoS ONE* 2014; **9**: e109565.
- 35 Gyimesi E, Sipka S, Danko K *et al*. Basophil CD63 expression assay on highly sensitized atopic donor leucocytes - a useful method in chronic autoimmune urticaria. *Br J Dermatol* 2004; **151**: 388–396.
- 36 Altrichter S, Peter HJ, Pisarevskaja D, Metz M, Martus P, Maurer M. IgE mediated autoallergy against thyroid peroxidase - a novel pathomechanism of chronic spontaneous urticaria? *PLoS ONE* 2011; **6**: e14794.
- 37 Metz M, Krull C, Hawro T *et al*. Substance P is upregulated in the serum of patients with chronic spontaneous urticaria. *J Invest Dermatol* 2014; **134**: 2833–2836.
- 38 Asero R. D-dimer: a biomarker for antihistamine-resistant chronic urticaria. *J Allergy Clin Immunol* 2013; **132**: 983–986.
- 39 Mlynek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M. How to assess disease activity in patients with chronic urticaria? *Allergy* 2008; **63**: 777–780.
- 40 Stull D, McBride D, Georgiou P, Zuberbier T, Grattan C, Balp M-M. Measuring patient severity in chronic spontaneous/idiopathic urticaria (CSU/CIU) as categorical health states: efficient and informative? *Allergy* 2014; **69**(Suppl 99): 317 (Abstract 826).
- 41 Weller K, Groffik A, Magerl M *et al*. Development, validation, and initial results of the Angioedema Activity Score. *Allergy* 2013; **68**: 1185–1192.
- 42 Weller K, Groffik A, Church MK *et al*. Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control. *J Allergy Clin Immunol* 2014; **133**: 1365–1372.
- 43 Baiardini I, Pasquali M, Braidò F *et al*. A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-QoL). *Allergy* 2005; **60**: 1073–1078.
- 44 Brzoza Z, Badura-Brzoza K, Mlynek A *et al*. Adaptation and initial results of the Polish version of the GA(2)LEN chronic urticaria quality of life questionnaire (CU-Q(2)oL). *J Dermatol Sci* 2011; **62**: 36–41.
- 45 Dias GA, Pires GV, Valle SO *et al*. Cross-cultural adaptation of the Brazilian-Portuguese version of the chronic urticaria quality-of-life questionnaire - CU-Q2oL. *Allergy* 2011; **66**: 1487–1493.
- 46 Kocaturk E, Weller K, Martus P *et al*. Turkish version of the chronic urticaria quality of life questionnaire: cultural adaptation, assessment of reliability and validity. *Acta Derm Venereol* 2012; **92**: 419–425.
- 47 Mlynek A, Magerl M, Hanna M *et al*. The German version of the Chronic Urticaria Quality-of-Life Questionnaire: factor analysis, validation, and initial clinical findings. *Allergy* 2009; **64**: 927–936.
- 48 Valero A, Herdman M, Bartra J *et al*. Adaptation and validation of the Spanish version of the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL). *J Investig Allergol Clin Immunol* 2008; **18**: 426–432.
- 49 Darlenski R, Kazandjieva J, Zuberbier T, Tsankov N. Chronic urticaria as a systemic disease. *Clin Dermatol* 2014; **32**: 420–423.
- 50 Gupta MA, Gupta AK, Schork NJ, Ellis CN. Depression modulates pruritus perception: a study of pruritus in psoriasis, atopic dermatitis, and chronic idiopathic urticaria. *Psychosom Med* 1994; **56**: 36–40.
- 51 Giménez-Arnau A, Maurer M, De La CJ, Maibach H. Immediate contact skin reactions, an update of Contact Urticaria, Contact Urticaria Syndrome and Protein Contact Dermatitis – “A Never Ending Story”. *Eur J Dermatol* 2010; **20**: 552–562.
- 52 Schoepke N, Mlynek A, Weller K, Church MK, Maurer M. Symptomatic dermographism: an inadequately described disease. *J Eur Acad Dermatol Venereol* 2015; **29**: 708–712.
- 53 Mlynek A, Vieira Dos SR, Ardelean E *et al*. A novel, simple, validated and reproducible instrument for assessing provocation threshold levels in patients with symptomatic dermographism. *Clin Exp Dermatol* 2013; **38**: 360–366.
- 54 Katsarou-Katsari A, Makris M, Lagogianni E, Gregoriou S, Theoharides T, Kalogeromitros D. Clinical features and natural history of acquired cold urticaria in a tertiary referral hospital: a 10-year prospective study. *J Eur Acad Dermatol Venereol* 2008; **22**: 1405–1411.
- 55 Mlynek A, Magerl M, Siebenhaar F *et al*. Results and relevance of critical temperature threshold testing in patients with acquired cold urticaria. *Br J Dermatol* 2010; **162**: 198–200.
- 56 Siebenhaar F, Degener F, Zuberbier T, Martus P, Maurer M. High-dose desloratadine decreases wheal volume and improves cold provocation thresholds compared with standard-dose treatment in patients with acquired cold urticaria: a randomized, placebo-controlled, crossover study. *J Allergy Clin Immunol* 2009; **123**: 672–679.
- 57 Altrichter S, Salow J, Ardelean E, Church MK, Werner A, Maurer M. Development of a standardized pulse-controlled ergometry test for diagnosing and investigating cholinergic urticaria. *J Dermatol Sci* 2014; **75**: 88–93.
- 58 Maibach HI, Johnson HL. Contact urticaria syndrome. Contact urticaria to diethyltoluamide (immediate-type hypersensitivity). *Arch Dermatol* 1975; **111**: 726–730.
- 59 Heinzerling L, Mari A, Bergmann KC *et al*. The skin prick test - European standards. *Clin Transl Allergy* 2013; **3**: 3.
- 60 Gruber BL, Baeza ML, Marchese MJ, Agnello V, Kaplan AP. Prevalence and functional role of anti-IgE autoantibodies in urticarial syndromes. *J Invest Dermatol* 1988; **90**: 213–217.