

How to Measure Disease Activity, Impact, and Control in Patients with Recurrent Wheals, Angioedema, or Both



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Learning objectives:

1. To understand the need for patient-reported outcome (PRO) measures in patients with recurrent wheals, angioedema, or both.
2. To learn which specific PRO measures are available for patients with recurrent wheals, angioedema, or both.
3. To recognize the importance of validation and minimal clinically important difference (MCID) when assessing utility of PRO measures.
4. To apply commonly used instruments in regular assessment of the patient with chronic spontaneous urticaria (CSU) and angioedema.

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Abbreviations used

AAS- Angioedema Activity Score
 AE-QoL- Angioedema Quality of Life Questionnaire
 AECT- Angioedema Control Test
 CSU- Chronic spontaneous urticaria
 CU-Q2oL- Chronic Urticaria Quality of Life Questionnaire
 DLQI- Dermatology Life Quality Index
 HAE- Hereditary angioedema
 HAE-AS- Hereditary Angioedema Activity Score
 HAE-QoL- Hereditary Angioedema Quality of Life
 HRQoL- Health-related quality of life
 MCID- Minimal clinically important difference
 PRO- Patient-reported outcome
 QoL- Quality of life
 UAS7- Urticaria Activity Score 7
 UCT- Urticaria Control Test

Chronic spontaneous urticaria and chronic inducible urticaria are characterized by wheals, angioedema, or both, whereas other conditions such as hereditary angioedema present only with angioedema. The unpredictability of outbreaks, disfigurement, pruritus, and associated sleep and work disturbance can cause a significant impact on quality of life (QoL). Significant breakthroughs in the understanding of these conditions in recent years have led to the development of novel therapies. Assessment of patients with these conditions not only focuses on the clinical activity of the condition, but also on the impact on QoL and disease control with treatment. Patient-reported outcome measures, especially if sufficiently validated, give due prominence to the patient's perspective regarding disease impact and treatment outcomes. This article will review the tools readily available to assess activity, impact, and control in patients with recurrent wheals, angioedema, or both. © 2021 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;9:2151-7)

Key words: Angioedema; Disease activity; Disease control; HAE; Quality of life; Patient-reported outcome; Urticaria

Urticaria with or without angioedema is one of the most common presenting complaints in dermatology and allergy/immunology practice with a general population prevalence of approximately 0.6% to 1%.¹ Currently, urticaria is classified according to duration and possible triggers. Chronic spontaneous urticaria (CSU), formerly also referred to as chronic idiopathic urticaria, is defined as wheals (hives) or angioedema or both, occurring for at least 6 weeks.

Angioedema is deep, localized, self-limited, and often recurrent swelling of the deep layers of the skin.²⁻⁴ When angioedema occurs without wheals, bradykinin-mediated conditions such as

hereditary angioedema (HAE) or angiotensin converting enzyme inhibitor-related angioedema must be excluded. Typical locations of angioedema include the face, lips, tongue, larynx, extremities, genitalia, and in the case of HAE also the abdomen.⁴

Although chronic urticarial conditions differ from some other chronic diseases by the absence of long-term organ damage and low mortality rates, they can be debilitating and distressing with major impacts on quality of life (QoL). This arises because of the unpredictability of the outbreaks and the disfiguring nature of the lesions, particularly when angioedema is present, as well as the intense pruritus with CSU that disturbs sleep and equilibrium. In fact, one study has demonstrated that the QoL impacts for patients with CSU are comparable with those seen in patients awaiting coronary artery bypass surgery.⁵ These aspects of the disease lead to psychological and emotional distress.^{6,7}

For these reasons, assessment of patients with CSU and recurrent angioedema must not only focus on the clinical aspects of the condition, but also on its impact on QoL and disease control with treatment. Patient-reported outcome (PRO) measures, especially if sufficiently validated, give due prominence to the patient's perspective regarding disease impact and treatment outcomes.

Before an instrument can be used in clinical practice or trials, a questionnaire must be shown to have reliability and validity, the latter of which refers to its "accuracy of measurement" within the context of the tool's outcomes of interest.⁸ The sensitivity to change and the minimal clinically important difference (MCID) are other important features of any instrument. The MCID is the smallest change in a score that can be considered clinically relevant.⁹

Dermatology life quality index

The best-known general dermatology-specific questionnaires are the 10-item Dermatology Life Quality Index (DLQI) for patients aged 16 and above and the children's version (CDLQI) for patients aged 4 to 16. The DLQI has been shown to be a valid, reliable, and clinically useful outcome measure for assessing QoL in patients with CSU.¹⁰ Subjects rate their dermatology symptoms and the impact of their skin condition on various aspects of their lives over the previous 7 days. The overall score ranges from 0 to 30 for both instruments (higher score meaning worse dermatology QoL). A DLQI/CDLQI score of >10 is relevant for a considerable impact on patients' life. The DLQI has been shown to correlate well with measures of urticaria disease activity as measured by other PROs.¹¹

Although non-disease-specific or general tools are useful, they often lack the specificity required to fully appreciate the impact of a particular condition. Thus, the objective of this review is to explore specific tools designed to measure disease activity and control of CSU, recurrent angioedema, and HAE.

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MEASURES FOR CSU

Disease activity

A number of measurement tools for CSU exist; some measure specific features of the condition, whereas others give a more global indication of disease activity.

The Weekly Itch Severity Score and the Weekly Hives Severity Score are 2 instruments that measure specific features of CSU.^{12,13} In reality, these instruments are not used in clinical practice as they do not encompass all features of the condition. Other specific features of CSU that impact on patients' lives such as sleep disturbance due to pruritus may be captured with tools such as the Weekly Sleep Interference Score and Insomnia Severity Index¹⁴⁻¹⁶; however, they too are rarely used in clinical practice as such measures do not capture all patient impacts of CSU. Measures that give a more global assessment of disease activity are needed to fully appreciate the true impact of CSU on patients' lives.

Weekly activity interference score. The Activity Interference Score measures the impact of CSU on the patient's daily activities.^{5,17} This score is a daily record by the patient on how much CSU interferes with his or her daily activities. It is scored on a scale from 0 (no interference) to 3 (severe interference). The weekly Activity Interference Score ranges from 0 to 21.

The urticaria activity score 7. Unlike other activity scores, Urticaria Activity Score 7 (UAS7) is a PRO measure used in clinical trials and routine care to evaluate the efficacy of CSU therapy. Target symptoms of CSU are pruritus and wheals. This self-assessment tool was derived from one used in rheumatoid arthritis for patients on nonsteroidal anti-inflammatories and was modified for patients with chronic urticaria to assess disease activity and treatment effects.^{18,19} The wheals and itch severity are scored from 0 to 3, with higher values indicating greater number and severity, respectively. The weekly UAS ranges from 0 to 42 (Table I).^{18,19}

Two versions of the UAS7 have been published: one that uses a once daily assessment and the other a twice daily assessment.^{18,19} From a practical perspective, a once daily scoring by the patient encourages greater compliance and participation.

Although the treatment paradigm previously focused on itch as the primary symptom of CSU, the current target of therapy in CSU treatment guidelines is to achieve complete freedom of signs and symptoms (UAS7 = 0).²

Limitations of the UAS include lack of inclusion of scoring for angioedema and the need for good patient compliance in completing a daily score for a period of time.

UAS7 scores should be measured during the observation, treatment, and post-treatment follow-up periods. The UAS7 was shown to be a valid tool. Studies have established the MCID as a range of 9.5 to 10.5 for UAS7.¹⁹

Chronic urticaria quality of life questionnaire. QoL is remarkably impacted in patients with CSU. Many available QoL questionnaires are not explicitly developed for patients with CSU. The Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) was created as a simple-to-administer and well-accepted tool by the responding patients.²⁰ CU-Q2oL is the only validated tool to evaluate disease-specific QoL impairments of patients with CSU. Studies have established the MCID for the

TABLE I. Urticaria disease states based on UAS7 scoring

Disease state	UAS7 score
Severe activity	28-42
Moderate activity	16-27
Mild activity	7-15
Well-controlled	1-6
Completely controlled	0

UAS7, Urticaria Activity Score 7.

CU-Q2oL score range from -3 for a small improvement to -19 for considerable improvement.^{21,22}

Disease control/response to medication

Urticaria control test. The Urticaria Control Test (UCT) is a validated tool that was designed to overcome some of the limitations of the UAS7.²³ It can be administered quickly in a clinical setting.

It comprises 4 brief questions. Unlike the UAS7, it gives a retrospective account of urticaria control over the previous 4 weeks without the need to keep a diary; it applies to patients with all types of urticaria. The questionnaire subjectively quantifies the patient's overall physical symptoms, impact on QoL, frequency of treatment inadequacy, and overall control of urticaria over the previous 4 weeks. Each question is scored from 0 to 4 and the maximum score is 16, which indicates full control of urticaria. This sensitive test for screening of urticaria uses a score of 12 or more to define well-controlled urticaria.

Following validation studies, a change of 3 points in an individual's UCT score is considered to be a relevant change in disease control.^{23,24} The UCT has only been tested in adults but has also been applied to children with urticaria. The simplicity of the UCT and its global applicability to all types of urticaria make it an excellent tool for measurement of disease control and response to medication.

MEASURES FOR RECURRENT ANGIOEDEMA

Disease activity

Angioedema activity score. The Angioedema Activity Score (AAS) was only recently developed and may be applied to all subtypes of recurrent angioedema, including HAE and CSU (Table II).²⁵ The AAS is a prospective PRO measure that is completed once daily by the patient, usually for at least 4 weeks (AAS28).²⁵ Patients are asked if they exhibited angioedema in the past 24 hours, and if affirmative, to answer 5 AAS questions on the duration, severity, and impact of the angioedema in the past 24 hours.²⁵ Answers are scored from 0 to 3 points, that is, the minimum and maximum daily AAS score is 0 and 15, respectively. In a validation study, the AAS showed high levels of validity and reliability.²⁶ The MCID was found to be 8 points for a 1-week documentation (AAS7).²⁶ The AAS has been applied successfully in several clinical trials in the field of urticaria and HAE.^{26,27}

The test has some limitations. The AAS is prospective, so a result is available only in a follow-up visit. Secondly, daily documentation requires a high level of patient adherence. Thirdly, scoring takes some time, a potential obstacle for its

TABLE II. Comparison of the Hereditary Angioedema Activity Score (HAE-AS) and Angioedema Activity Score (AAS), as well as the Hereditary Angioedema Quality of Life (HAE-QoL) tool and Angioedema Quality of Life (AE-QoL) tool

Item	HAE-AS	AAS	HAE-QoL	AE-QoL
No. of items	12 (once)	1-6 (everyday)	25 (once)	17 (once)
Recall period	6 mo	1 d	6 mo	4 wk
Applicable in HAE type 1/2	+	+	+	+
Applicable in other forms of recurrent angioedema	—	+	—	+
High level of patient compliance required	—	+	—	—
Minimal clinically important difference published	—	+	—	+
Cost-free use in routine management and investigator-initiated clinical research	+	+	+	+
Disease-specific (HAE)	+	—	+	—
Validated	+	+	+	+

TABLE III. Patient-reported outcome measures in patients with recurrent wheals, angioedema, or both

Item	UAS	CU-Q2oL	UCT	AAS	AE-QoL	AECT	HAE-AS	HAE-QoL	HAEA-QoL
Applicable in patients with CSU with wheals but no angioedema	+	+	+	—	—	—	—	—	—
Applicable in patients with CSU with wheals and angioedema	+	+	+	+	+	+	—	—	—
Applicable in patients with CSU with angioedema and no wheals	—	(+)	(+)	+	+	+	—	—	—
Applicable in patients with hereditary angioedema	—	—	—	+	+	+	+	+	+
No. of items	2	23	4	5	17	4	12	25	27
Prospective assessment (time period)	+ (daily for 7 d)	—	—	+ (daily for at least 28 d)	—	—	—	—	—
Retrospective assessment (recall period)	—	+ (2 wk)	+ (4 wk)	—	+ (4 wk)	+ (4 wk 3 mo)	+ (6 mo)	+ (6 mo)	+ (not published)
Sensitivity to change	+	+	+	+	+	Currently under examination	Unknown	Unknown	Unknown
MCID	11	3 and 15	3	8	6	Currently under examination	—	—	—
Cost-free for									
Patient management	+	+	+	+	+	+	+	+	Unknown
Academic research	+	+	+	+	+	+	+	+	
Industry studies	+	—	—	—	—	—	—	—	
Available in multiple languages	+	+	+*	+*	+*	+*	+†	+†	—

AAS, Angioedema Activity Score; AECT, Angioedema Control Test; AE-QoL, Angioedema Quality of Life Questionnaire; CSU, chronic spontaneous urticaria; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; HAE-AS, Hereditary Angioedema Activity Score; HAEA-QoL, Hereditary Angioedema Association Quality of Life; HAE-QoL, Hereditary Angioedema Quality of Life; MCID, minimal clinically important difference; UAS, Urticaria Activity Score; UCT, Urticaria Control Test.

*For details with regard to available language versions of the AAS, AE-QoL, UCT, and AECT, go to www.moxie-gmbh.de (additional language/country versions may be or are in preparation; for more information please contact MOXIE at info@moxie-gmbh.de).

†For details with regard to available language versions of the HAE-AS and HAE-QoL, go to www.idipaz.es.

application in routine care. Finally, there is no version available for children and adolescents. For these reasons, the AAS is usually considered to be a helpful tool for clinical studies, and although complex, an electronic version has made it acceptable for many clinicians.

Disease control/response to medication

Angioedema control test. Given the unpredictable and recurrent nature of angioedema attacks, measurement of disease control has been made possible with publication of the Angioedema Control Test (AECT).²⁸ It contains 4 questions and

TABLE IV. Unmet needs regarding CSU and HAE-specific tools

- The lack of validated tools for children and adolescents. As of yet there is no single disease-specific validated tool available for CSU, recurrent angioedema, and HAE to assess disease activity, impact, or control. In this age group, the generic tools such as the CDLQI are the only way to go at the moment
- Availability of all tools in as many languages as possible
- Availability of digital versions of all the tools (that are broadly available for routine patient care)
- The retrospective HAE-specific instruments span a large period of time, which may lead to recall challenges for patients
- Only 1 HAE-specific instrument (HAE-QoL) encompasses both disease activity and HRQoL
- There are a lack of studies describing the MCID and sensitivity to change measurements for HAE-specific instruments

CDLQI, Children's Dermatology Life Quality Index; *CSU*, chronic spontaneous urticaria; *HAE*, hereditary angioedema; *HAE-QoL*, Hereditary Angioedema Quality of Life; *HRQoL*, health-related quality of life; *MCID*, minimal clinically important difference.

is available in 2 versions, either with a recall period of 4 weeks or 3 months. Both versions are identical and yield largely similar results.²⁹ Questions address frequency of symptoms, QoL impairment, unpredictability of episodes, and the level of control achieved by current therapy.²⁸ Response options are presented as a 5-point Likert scale and scored from 0 to 4 points. The minimum and maximum score of the AECT is 0 and 16, respectively. The higher the score the better the level of angioedema control. The published validation study demonstrated high levels of internal consistency and test-retest reliability.²⁹ A cutoff value of 10 points has been found to best distinguish patients with poorly versus well-controlled disease, that is, patients with 10 points or more can be considered to have well-controlled recurrent angioedema.²⁹ The responsiveness of the AECT, including its MCID, is currently being investigated.

Limitations of the AECT include lack of deeper insights into the frequency and impact of recurrent angioedema and no version for children and adolescents. Strengths of the AECT are its brevity and clear results. It is easy to administer, score, and interpret making it particularly useful in daily patient care.²⁹

Quality of life

Angioedema quality of life questionnaire. The Angioedema Quality of Life Questionnaire (AE-QoL) was first published almost 10 years ago as the first symptom-specific PRO measure to assess angioedema-specific QoL impairment.³⁰ It consists of 17 questions (Table II). Each question covers the previous 4 weeks and consists of 5 answers scored from 0 to 4. The individual question scores can be summed up as a total score and 4 domain scores: "Functioning," "Fatigue/Mood," "Fears/Shame," and "Nutrition."³¹ The AE-QoL has proven validity and reliability.³¹ In a subsequent study on its responsiveness, the MCID of the AE-QoL was found to be 6 points.³¹ A recent validation study of the Thai version of the AE-QoL confirmed its high levels of validity and reliability and suggested a score of ≥ 39 to indicate a moderate-to-large effect of recurrent angioedema on patients' lives.³² The AE-QoL has been successfully applied in several clinical studies in the field of chronic urticaria and HAE and has provided useful data on the improvement of recurrent angioedema-related QoL impairment by novel treatments.³³⁻³⁷ Compared with the AECT, the respondent burden of the AE-

QOL is slightly higher and the score computation and interpretation is more complex. On the other hand, the AE-QoL provides a more detailed insight into the impact of recurrent angioedema on different aspects of health-related quality of life (HRQoL). A version for children and adolescents is not available yet.

MEASURES FOR HEREDITARY ANGIOEDEMA

Disease activity

There are currently 2 validated PRO instruments to evaluate disease activity for HAE: The Hereditary Angioedema Activity Score (HAE-AS) and the AAS.^{25,38} Although not specific to HAE, the AAS has been used in randomized clinical trials involving emerging therapies for HAE, such as oral plasma kallikrein inhibitors (avoralstat and berotralstat), to measure disease activity.^{27,34} A comparison of the HAE-AS and AAS is shown in Table II.

The hereditary angioedema activity score. The HAE-AS is a retrospective tool that was developed from the clinical self-administered HAE questionnaire, from which questions were selected based on literature review and discussions with clinicians and patients.³⁸ The final HAE-AS contains 12 questions that patients evaluate over the past 6 months, including those on the frequency of specific HAE symptoms and attacks, number of treated attacks, emergency visits, psychological treatment, and missed school or work.³⁸ It also asks patients about their general health and impairment of everyday activities within the past month.³⁸ Statistical analyses showed that the HAE-AS measurement tool has good discriminative validity and is reliable.³⁸ This tool has not yet been used in published clinical trials.

Quality of life

The Canadian International HAE guideline recommends routinely assessing the HRQoL of patients, using validated instruments, as an important component of HAE management.³⁹ There are currently 2 validated retrospective instruments designed to evaluate recurrent angioedema HRQoL: the Hereditary Angioedema Quality of Life (HAE-QoL) tool and AE-QoL tool.^{30,40} Although not specific to HAE, the AE-QoL has been used in clinical practice and trials of HAE therapies.^{26,34,35,37,41}

Hereditary angioedema quality of life. Development of the HAE-QoL involved semistructured patient interviews, which underwent qualitative content analysis, expert and patient feedback, cross-cultural adaptation, pilot testing in 18 countries, and a reduction process.^{40,42} The final HAE-QoL includes 25 items and 7 dimensions ("treatment difficulties, physical functioning and health, disease-related stigma, emotional role and social functioning, concern about offspring, perceived control over illness, and mental health").⁴² Statistical analyses showed that the HAE-QoL is reliable with good discriminant and convergent validity.⁴² In an observational study of plasma-derived nano-filtered C1-INH for IV use (Berinert), the HAE-QoL was shown to be nonresponsive.^{39,43} The HAE-QoL has been used in a clinical setting to assess the HRQoL of patients with HAE.⁴⁴⁻⁴⁶

Disease control/response to medication

Angioedema control test. Until the recent development of the AECT, there was no tool to measure disease control for

recurrent angioedema, including HAE, yet the 2017 WAO/EAACI guideline on HAE recommended PRO instruments to assess disease control.^{3,28} As previously described, the AECT has been shown to be a valid and reliable tool,²⁹ and should be used alongside PRO instruments for HAE disease activity.

CONCLUDING REMARKS

In the absence of laboratory parameters to objectively measure activity of urticaria, validated PRO measures are useful to quantify activity, control and disease impact, inform treatment, and assess responses in both clinical and research settings.

Urticaria and angioedema-specific tools are now available and validated for all aspects—disease activity, disease control, and angioedema-related QoL impairment. These tools can help to improve and standardize assessment and documentation of the patient's disease status and changes in response to treatment (Table III).

HAE is a complex disease characterized by periods of remission and acute attacks of angioedema; hence disease activity and control may be difficult to capture. Its impact on HRQoL can be considerable. Current HAE guidelines recommend that health care providers not only monitor HAE control as it relates to frequency, duration, and severity of attacks, but routinely assess HRQoL using validated instruments to optimize HAE management. However, unmet needs exist regarding the assessment of disease activity and HRQoL of HAE (Table IV). Specifically, the HAE-AS and HAE-QoL are limited in scope, involve a lengthy recall period, and have not been researched with regard to MCID or sensitivity to change. These instruments have yet to be validated for use in children, translated into all languages for global studies, and adapted for electronic use. With regard to emerging tools in this field, the Hereditary Angioedema Association QoL was developed to measure the HRQoL of patients with HAE in the United States where studies to assess its validity and reliability are underway.⁴⁷

In an era where telehealth is becoming more widely applied, the various instruments discussed above can be adapted for use on smartphones and web-based applications, enabling electronic transfer to the treating physician for monitoring patient outcomes and obviating the need for face-to-face consultation under certain circumstances.

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