

# Assessment of Severity and Quality of Life in Chronic Urticaria

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## ■ Abstract

Chronic urticaria (CU) is very prevalent in the general population and, despite its low mortality, can have devastating effects on the quality of life (QoL) of those who experience it. Therefore, consensus documents on its classification, diagnosis, and treatment have become a necessity. The intensity of urticaria is currently evaluated using indices such as the Urticaria Activity Score and visual analog scales to assess itch or the degree of itch associated with the use of antihistamines. QoL is evaluated using various generic questionnaires and specific tools for skin disease and for CU. In recent years, attempts have been made to combine these evaluations to create a specific tool that would enable us to simultaneously evaluate the severity of the condition and the impact of symptoms on QoL. One such tool is the Urticaria Severity Score, which also allows us to compare global changes brought about by different treatments.

**Key words:** Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL). Dermatology Life Quality Index (DLQI). Visual analog scale (VAS). Itch Intensity Scale. Medical Outcome Study 36-Item Short Form Health Survey (SF-36). Nottingham Health Profile (NHP). Satisfaction Profile (SAT-P). Skindex-29. Chronic urticaria. Urticaria Activity Score (UAS). Urticaria Severity Score (USS). VQ-Dermato. World Health Organization Quality of Life Assessment-Brief (WHOQOL-BREF). Work Productivity and Activity Impairment (WPAI).

## ■ Resumen

La urticaria crónica (UC) es una enfermedad muy prevalente en la población general, que a pesar de su baja mortalidad puede resultar devastadora para la calidad de vida (CdV) de quien la sufre, y que ha hecho necesario establecer documentos de consenso sobre su clasificación, diagnóstico y tratamiento. La valoración objetiva de la intensidad de la urticaria se ha venido haciendo a través de índices como el *Urticaria Activity Score*, las escalas analógicas visuales del prurito o el nivel de prurito asociado al empleo de antihistamínicos. La valoración de la calidad de vida se ha medido a través de distintos cuestionarios genéricos, específicos de enfermedad cutánea y específicos de UC. En los últimos años, se intenta aunar de algún modo todas estas herramientas de evaluación, en índices específicos que nos permitan valorar a un tiempo gravedad e impacto vital de los síntomas en la UC, como el denominado *Urticaria Severity Score*, y comparar así los cambios globales en relación con distintos tratamientos.

**Palabras clave:** Calidad de vida. Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL). Dermatology Life Quality Index (DLQI). Escala analógica visual (EVA). Itch Intensity Scale. Medical Outcome Study 36-Item Short Form Health Survey (SF-36). Nottingham Health Profile (NHP). Satisfaction Profile (SAT-P). Skindex-29. Urticaria crónica. Urticaria Activity Score (UAS). Urticaria Severity Score (USS). VQ-Dermato. World Health Organization Quality of Life Assessment-Brief (WHOQOLBRIEF). Work Productivity and Activity Impairment (WPAI).

## Introduction

Urticaria is one of the most frequent presenting complaints in dermatology, allergy, and emergency departments. The term chronic urticaria (CU) is understood as the appearance of recurrent wheals more than twice a week for over 6 consecutive weeks [1]. According to one population study [2], the prevalence of CU in Spain was estimated to be 0.6%. Difficulties reaching an etiological diagnosis, the absence of biological follow-up and monitoring markers, and the lack of a gold standard therapy have led to the development of different consensus documents on the classification, diagnosis, and therapeutic management of CU [3,4].

Objective evaluation of the intensity of urticaria has generally been based on dissimilar symptom rating scales. This approach hinders both epidemiological studies and the comparison of clinical trial findings. Therefore, the recent consensus guidelines from the European Academy of Allergology and Clinical Immunology, Global Allergy and Asthma European Network, European Dermatology Forum, and World Allergy Organization (EAACI/GA2LEN/EDF/WAO) [3] recommend using a direct well-established scale such as the Urticaria Activity Score (UAS), which evaluates the main disease characteristics (itch, presence, and number of wheals) on a Likert-type symptom intensity scale (0 to 3), with a total daily score ranging from 0 to 6 (Table 1) [5]. The UAS has been used in numerous controlled clinical trials and in daily clinical practice. It was recently validated specifically for the follow-up and monitoring of CU activity [5], with the explicit recommendation that it would be used for at least 4 consecutive days or, preferably, for 1 week (UAS 7).

Table 1. Urticaria Activity Score

Score	Wheals or hives	Itch
0	None	None
1	Mild (<20 wheals/24 h)	Mild
2	Moderate (21-50 wheals/24 h)	Moderate
3	Intense or severe (>50 wheals/24 h or large confluent areas of wheals)	Intense or severe

Scoring 0-6

Visual analog scales (VAS) have also been used in both adult and pediatric populations and have been validated for assessment of the severity, or intensity, of symptoms. A Spanish version of the Itch Intensity Scale was recently validated, and both an adult and a pediatric version are available [6].

CU symptoms (eg, itch and wheals) affect a wide range of daily activities, from personal care to sleep/rest, work performance, and social relationships. Physical and emotional functioning is subjectively impaired beyond the severity of the actual disease symptoms. As with other chronic skin diseases, proper assessment of the health-related quality of life (HRQoL, or QoL) using appropriate tools is at least as important in estimating progression as objectively quantifying the intensity of symptoms. Various indices and questionnaires (including both generic and specific tools for assessing skin

disease) have been used to assess QoL in CU (Table 2) [7]. A CU-specific QoL questionnaire, the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) [8], has been validated in Spanish [9]. Efforts are also being made to combine these assessment tools into a specific index that would allow us to simultaneously evaluate the severity and impact of CU symptoms on QoL and thus compare responses to various treatments. Such is the objective of the Urticaria Severity Score (USS) [10].

Table 2. Tools Most Commonly Used to Measure Quality of Life in Chronic Urticaria

### Generic questionnaires

- Medical Outcomes Survey Short Form-36 (SF-36)
- Medical Outcomes Survey Short Form-12 (SF-12)
- Nottingham Health Profile (NHP)
- Satisfaction Profile (SAT-P)
- Euro-QoL
- WHO QoL Assessment-Brief (WHOQOL-BREF)
- Work Productivity and Activity Inventory (WPAI-AS)

### Specific skin disease questionnaires

- Dermatology Quality of Life Index (DQLI)
- Children's Dermatology Life Quality Index (CDLQI)
- Dermatology Quality Of Life Scales (DQOLS)
- Dermatology-Specific Quality of Life (DSQL)
- Skindex-29
- Skindex-16
- VQ-Dermato

### Specific chronic urticaria questionnaires

- Chronic Urticaria and Quality of Life Questionnaire (CU-Q2oL)
- Urticaria Severity Score (USS)

## Chronic Urticaria: Definition and Characteristics

CU is defined as the recurrence of wheals more than twice a week for a period of 6 weeks or longer [1]. CU also has a number of other characteristics [11]:

- Wheals lasting more than 1 hour (unlike simple dermatographic urticaria) and less than 24-36 hours (unlike urticarial vasculitis). Lesions may be indurated and painful.
- The natural course of the disease varies greatly with outbreaks and remissions that can last from a few months to more than 20 years.
- Major repercussions on QoL that are considered equivalent to those in severe coronary disease [12,13].
- No underlying food or drug allergies.

Considering histopathological features, CU is characterized by a perivascular infiltrate, without vasculitis or immune

deposits, constituted by CD4<sup>+</sup> cells with mixed T<sub>H</sub>1/T<sub>H</sub>2 characteristics, monocytes, and variable quantities of polymorphonuclear cells, eosinophils, and basophils that form a late-phase infiltrate. Peripheral basopenia and eosinophil activation products (major basic protein or eosinophil cationic protein) may be present, as may adhesion molecules (integrins and selectins), thus demonstrating endothelial cell activation [14].

CU is divided into inducible urticaria (triggered by specific physical stimuli) and spontaneous (or idiopathic) urticaria [15]. In at least one-third of idiopathic presentations, the etiology is autoimmune and could be associated with thyroid autoimmunity, with or without clinical hypothyroidism [16]. As well as presenting antithyroid antibodies more frequently than the general population [16], CU patients may have IgG antibodies targeting circulating IgE or (much more often) the  $\alpha$  subunit of the IgE high-affinity receptor (Fc $\epsilon$ RI) [17]. These antibodies can be detected by skin testing with autologous serum—although the results are poorly reproducible owing to high variability depending on who performs the test [18]—or by demonstrating healthy basophil degranulation *in vitro* in serum [19]. In addition, immunoblotting with patient serum can reveal a 30- to 35-kDa IgG-binding band corresponding to the  $\alpha$  subunit of Fc $\epsilon$ RI. These antibodies may be present in other autoimmune processes such as lupus or dermatomyositis, although in autoimmune CU they correspond to the IgG1 or IgG3 subclass, which is capable of activating complement and generating anaphylotoxins such as C5a. In other words, they are functional, a characteristic that is considered to be specific of autoimmune CU [20].

## Objective Evaluation of the Intensity of Urticaria

Evaluating the intensity of urticaria is complicated because its signs and symptoms can vary significantly over a relatively short period of time. Furthermore, as the severity of CU has been evaluated using an array of very different symptom score scales, it is difficult to compare the results of clinical trials and epidemiological studies [21].

The current EAACI/GA2LEN/EDF/WAO consensus guidelines [3] recommend using simple well-established scales such as the UAS, which evaluates the basic characteristics of CU (itch and presence and number of wheals) in a Likert-type symptom intensity scale ranging from 0 to 3 (Table 1) [5]. Daily intensity of itch (ranging from 0 [none] to 3 [severe]) and number of wheals (ranging from 0 [none] to 3 [more than 12]) are summed to create a daily UAS score (ranging from 0 to 6 points per day). An enhanced version of the UAS was recently proposed and validated [22] and includes size of the largest hive (recorded on a scale ranging from 0 [none] to 3 [ $>2.5$  cm]) as another measure of disease activity.

The UAS has been used in numerous controlled clinical trials and in routine practice for daily clinical monitoring. In addition, it was recently validated for specific use in the follow-up and monitoring of CU activity [5]. Since the UAS can change from one day to another, various authors recommend using the sum of the UAS scores over 4 consecutive days

(UAS 4) [5] or over 7 days (UAS 7) [23] to compensate for these fluctuations.

Activity scales have been proposed to integrate symptom intensity and its impact on daily life. Jariwala et al [10] published an activity evaluation scale, the Urticaria Severity Score (USS), consisting of 9 questions that a patient responds to using a Likert-type scale (0 to 7). The USS combines purely quantitative data on CU activity, such as the number and location of wheals, with other data from classic QoL questionnaires, such as the number of days CU interferes with sleep or daily work or social activities. The USS compares CU activity with that of the previous week. Furthermore, Mathias et al [24] developed a daily diary for patients that included the UAS in conjunction with QoL measures such as interference with sleep, interference with daily activities, and symptom occurrence and management.

VAS have been used for many years to evaluate the severity or intensity of very variable symptoms that are difficult to measure objectively, such as pain [25,26]. These have been validated in both adults and children and consist of a line drawn on paper with zero at one end (symptom-free) and another number (1, 10, or 100) at the other end (worst case scenario). The line may be subdivided or numbered. VAS can be used to determine symptom changes in the same individual, but not to compare symptoms between different persons. In CU, VAS has mainly been used to evaluate the itch intensity and sedation levels with various antihistamines [27].

In practice, most authors consider the UAS, USS, and VAS as complementary tools for measurement of QoL [5].

## Quality of Life Measures in Urticaria

QoL refers to the functional effects of an illness and its treatment from the patient's perspective. It is therefore a subjective concept that has gained clinical and economic importance over the past decade and is now a fundamental indicator in all chronic diseases and in the comparative effectiveness of different treatments. QoL is particularly important in allergic conditions, especially urticaria, which is a chronic condition associated with low mortality. However, the high prevalence of urticaria and its considerable impact on the daily life of affected patients make it an economic and social burden. QoL is already assessed in the clinical monitoring of patients with urticaria and is used extensively in various settings, from clinical trials—assessment of CU is required by regulatory agencies in accordance with current legislation—to pharmaco-economic studies.

QoL is classically defined as the "the functional effect of a medical condition and/or its consequent therapy upon a patient, from the patient's perspective" [28]. The tools used to measure these effects in the case of CU comprise existing QoL questionnaires (Table 2) [7]. It is universally accepted that all QoL questionnaires must comply with the basic psychometric conditions of *feasibility* (reasonable length and patient-friendly), *validity* (measure what they are supposed to measure and distinguish symptom severity relative to the scores), *reliability* (reproducible and consistent with no contradictory responses), and sensitive to change (capable of detecting changes in symptoms following a given treatment) [29].

The QoL questionnaires used in CU can be classed as generic and specific. Generic questionnaires evaluate general QoL aspects in different populations and are applicable to various diseases and therapeutic interventions, thus enabling comparison of results. Specific questionnaires, on the other hand, provide details on relevant disease-related factors in a population; therefore, the results are useful in comparing different medicines, but they do not enable between-disease comparisons [7,29]. Although specific skin disease questionnaires have been used in CU, a specific questionnaire, the CU-Q2oL, was designed in 2005 [8]. Our group validated the Spanish version [9]. Table 3 shows the main use of each QoL assessment tool in CU.

Over the past two decades, many studies have compared the QoL of patients with CU to that of healthy controls, patients with respiratory allergies, and other seriously ill patients, such as those awaiting heart surgery [12], using either generic tools

Table 3. Principal Uses of Each Type of Quality of Life (QoL) Assessment Tool in Chronic Urticaria (CU)

	Generic Tools	Specific Dermatology Tools	Specific CU Tools
Comparison of QoL across various diseases	+++	-	-
Comparison of QoL across various skin diseases	+	+++	-
Comparison of QoL in different subpopulations of urticaria	+	++	+++
Monitoring QoL over time	+	++	+++
Monitoring QoL with treatments	+	++	+++

(SF-36, Satisfaction Profile [SAT-P], the Nottingham Health Profile [NHP]) or specific skin disease tools (Dermatology Quality of Life Index [DLQI], Skindex-29) (Table 4).

#### Evaluating Quality of Life in Chronic Urticaria Using Generic Instruments

The most widely used generic questionnaire is the Short Form 36 Health Survey (SF-36), which consists of 36 questions covering 8 domains grouped into 2 main areas: physical and mental [30]. Comparisons between patients with CU and patients with allergic respiratory disease using a generic questionnaire such as the SF-36 and the SAT-P indicate that daily life is more affected in patients with CU than in patients with rhinitis and/or asthma in aspects such as sleep, eating habits, work activity, and general physical and psychological functioning [31]. When generic questionnaires (such as the NHP) are used to compare CU to other diseases, the subjective limitations with CU were at least similar to those in patients with severe ischemic heart disease awaiting aorto coronary surgery [12]. Other studies comparing CU patients with healthy controls using generic instruments, such as the SF-36, found significantly lower scores in patients with CU in all domains separately. Engin et al [32] compared CU patients with healthy controls using the generic World Health Organization Quality of Life Assessment-Brief (WHOQOL-BREF) questionnaire and found significantly lower scores in the physical and mental subdomains and higher levels of anxiety and depression in CU patients, with an inverse correlation with QoL scores.

#### Evaluating Quality of Life in Chronic Urticaria Using Specific Skin Disease Instruments

The most widely used questionnaire in most clinical trials on CU is the DLQI [33], which consists of 10 questions

Table 4. Quality of Life (QoL) Studies in Patients With Chronic Idiopathic Urticaria (CIU)

Patients Study tools	Result	Reference
73 patients with CIU 34 healthy controls <i>World Health Organization Quality of Life Assessment-Brief (WHOQOL-BREF)</i>	CIU: Significantly lower scores in physical and mental subdomains	Engin et al (2008)
84 patients with CIU 75 healthy controls <i>Medical Outcomes Survey Short Form (SF-36)</i>	CIU: Significantly lower scores in all domains	Özkan et al (2007)
100 patients with CIU 96 healthy controls <i>Skindex-29</i>	CIU: Significantly lower scores in all domains	Staubach et al (2006)
21 patients with CIU 27 patients with respiratory allergy <i>Medical Outcomes Survey Short Form (SF-36)</i> <i>Satisfaction Profile (SAT-P)</i>	CIU: - Greater sleep disturbance - Greater disruption of work activity - Worse general physical and mental functioning	Baiardini et al (2003)
170 consecutive patients with chronic urticaria <i>Dermatology Life Quality Index (DLQI)</i>	All forms of chronic urticaria affect QoL	Poon et al (1999)
142 patients with CIU 98 patients with life-threatening heart disease <i>Nottingham Health Profile (NHP)</i>	Similar QoL scores in both groups	O'Donnell et al (1997)

subdivided into 6 domains (symptoms and feelings, daily activities, leisure, work/school, personal relationships, and treatment). Each question is scored on a scale of 0 to 3 (ranging from 0 [not at all] to 3 [very much]). The DLQI is calculated by summing the score of each question with a maximum of 30 and a minimum of 0; the higher the score, the worse the QoL. In addition to demonstrating its usefulness in assessing the most prevalent chronic skin diseases, the DLQI has been specifically validated for CU [34]. It has also been used to compare CU with other skin diseases, revealing a degree of impairment of QoL in CU similar to that of atopic dermatitis and worse than that of other skin diseases such as psoriasis, acne, vitiligo, or Behçet disease [35].

A prospective cross-sectional study of 1356 adult outpatients using the specific French VQ-Dermato questionnaire (an instrument that separately explores 7 components of QoL in 28 items or questions and that has been validated in adults with skin diseases) [36] compared the QoL profiles in CU (n=466), psoriasis (n=464), and atopic dermatitis (n=426). The impact of the 3 diseases on QoL was very different: psoriasis and atopic dermatitis had a greater impact on self-perception, social life, and leisure activities, while patients with CU and atopic dermatitis were more affected in terms of skin lesions and daily activities than patients with psoriasis. The psychological impact did not seem to differ between the 3 cases [37].

Skindex-29 is a specific questionnaire used to measure QoL via 29 items in 3 separate domains (symptoms, activity, and emotions) that has been validated in Spanish for skin disease [38]. A recent on-line survey of 321 randomly selected adult patients with CU using the Skindex-29 questionnaire showed major impairment in the activity domain (how urticaria affects daily life in areas such as sleep, work, school, and social life) and in the emotions domain (effects of urticaria in areas such as boredom, frustration, shame, anger, anxiety, and depression). The major functional impact was on sleep, with over 55% of patients reporting late evening/nighttime symptoms and an average involvement of 4 nights/week during an outbreak [39]. Another study based on the Skindex-29 questionnaire showed higher scores (worse QoL) in patients with CU assessed taking into account concomitant psychiatric disorders (anxiety, depression, or somatization disorders) [40]. Questionnaires such as the DLQI or Work Productivity and Activity Impairment (WPAI) questionnaires have revealed that sleep disruption could lead to a loss of productivity at work or school of up to 30% [41].

### *Evaluating Quality of Life in Chronic Urticaria Using Specific Chronic Urticaria Tools*

The only specific CU questionnaire developed to date is CU-Q2oL, which consists of 23 questions or items grouped into 6 QoL categories associated with the disease: itch (2 questions), swelling (2 questions), activities (6 questions), sleep (5 questions), limitations (3 questions), and looks (5 questions) [8]. It has been shown to be reproducible and sensitive to change, and has been validated in Spanish. For the validation, the Spanish version of CU-Q2oL was coadministered together with the Skindex-29 in a multicenter, observational, longitudinal study (695 patients), in which the

instrument was able to discriminate between groups with different levels of clinical severity [9].

The CU-Q2oL has also been validated in German [42], Polish [43], Turkish [44], and Brazilian Portuguese [45]. In the first 3 language versions, multiple regression analysis was used to group the questions into 6 QoL categories or domains adapted for cross-cultural validation that were different from the original: sleep (4 questions), activities (6 questions), itch/discomfort (4 questions), mental state (3 questions), swelling/food (4 questions), and looks or appearance/image (2 questions). The Brazilian version has 3 categories: sleep/mental state/food (8 questions), itch/impact on daily activities (8 questions), and swelling/limitations/appearance (7 questions). All versions were shown to meet the necessary psychometric conditions of validity, internal consistency, and sensitivity to change.

## **Unmet Needs**

A recent trend in CU is the attempt to obtain instruments that can be used to categorize patients globally, in other words, by jointly assessing symptom severity, the impact of such symptoms on specific daily activities, and the use of symptomatic medication. The previously mentioned USS was developed for this purpose. The USS is a mixed instrument consisting of 8 questions answered on a Likert-type scale of 0 to 7, plus 1 question on the location of wheals. After comparison with the DLQI and validation in 80 patients, the USS was found to be more sensitive in evaluating symptom severity, with no significant differences in the overall assessment of QoL [10].

According to a recent study by the Global Allergy and Asthma European Network (GA2LEN) on this matter [44], assessment of patients with CU should be based on disease progression as reported by patients in terms of both symptoms (using the UAS) and the impact of the symptoms on QoL (preferably using the CUQ2oL in settings where this is available). However, the same working group did recognize current limitations:

- Lack of specific tools to evaluate chronic urticaria in children and adolescents (self-evaluation or by parents) or inducible (physical) urticaria
- Lack of evaluation of the impact of the doctor/patient relationship during the course of CU
- Lack of an estimation of the minimal important difference for QoL tools in CU to be able to categorize the disease as mild, moderate, or severe
- No analysis of the relationship between the course of CU and psychological variables (eg, mood, stress, alexithymia, and psychiatric comorbidity).
- Cross-validation of tools to measure QoL in CU in various languages and cultures throughout the world.

## **Conclusions**

CU is a disease whose signs and symptoms vary greatly over time. It is chronic, insidious, and considerably affects the QoL of patients who experience it. Among the various tools developed to objectively measure the activity of CU,

there is broad consensus on the use of the UAS. While many generic and specific instruments can be used to assess the QoL of patients with CU, expert groups recommend using the only existing specific questionnaire, the CU-Q2oL, which has been validated in Spanish and shown to be reproducible and sensitive to change. Other instruments that may prove useful in clinical practice include the USS, which can be used to categorize patients globally, that is, by jointly assessing symptom intensity, the impact of symptoms on daily life, and the use of medication. VAS can be used to estimate specific aspects of the disease, such as itch or degree of sedation associated with treatment.

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### Conflicts of Interest

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