



# The challenges of chronic urticaria part 1: Epidemiology, immunopathogenesis, comorbidities, quality of life, and management

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## ABSTRACT

This is Part 1 of an updated follow-up review of a World Allergy Organization (WAO) position paper published in 2012 on the diagnosis and treatment of urticaria and angioedema. Since 2012, there have been advances in the understanding of the pathogenesis of chronic urticaria, and greater experience with the use of biologics, such as omalizumab, in patients with severe refractory disease. For these reasons, the WAO decided to initiate an update targeted to general practitioners around the world, incorporating the most recent information on epidemiology, immunopathogenesis, comorbidities, quality of life, clinical case presentations, and the management of chronic spontaneous and chronic inducible urticaria, including urticaria in special situations such as childhood and pregnancy. A special task force of WAO experts was invited to write the different sections of the manuscript, and the final document was approved by the WAO Board of Directors. This paper is not intended to be a substitute for current national and international guidelines on the management of urticaria and angioedema but to provide an updated, simplified guidance for physicians around the world who manage patients with this common ailment.

**Keywords:** Angioedema, Chronic inducible urticaria, Chronic spontaneous urticaria, Omalizumab Treatment, Urticaria

## INTRODUCTION

Chronic spontaneous (idiopathic) urticaria (CSU), defined as the occurrence of wheals, angioedema,

or both for more than 6 weeks, affects 1-2% of the population.<sup>1</sup> It is more prevalent in women and represents an important burden that compromises patient's quality of life, interferes with routine daily activities,<sup>2</sup> and frequently is associated with psychiatric comorbidities (depression and/or anxiety).<sup>3</sup> Mean yearly direct and indirect costs of CSU in the United States have been estimated to be \$244 million, with medication costs accounting for 62.5% and work absenteeism for 15.7% of the expenses.<sup>4</sup> Although the mechanisms leading to CSU are not completely understood at the present time, important pathophysiologic advances have been accomplished in recent years. It is thought

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that CSU is a chronic inflammatory skin disease in which various inflammatory cells and mediators are involved. This knowledge has permitted the envisioning of precise and personalized approaches for the management of this complex disease. As investigators discern immunologic pathways involved in the pathogenesis of CSU, novel therapeutic agents directed to specific molecular targets are being proposed.

In 2012 WAO published a position paper on the diagnosis and treatment of urticaria with a global vision.<sup>5</sup> Since that document was published, there have been advances in the understanding of the pathogenesis of chronic urticaria, and greater experience with the use of biologics, mainly omalizumab, in patients with severe disease. For these reasons, WAO decided to initiate an updated review of that paper targeted to general practitioners around the world, incorporating the most recent information on epidemiology, immunopathogenesis, comorbidities, quality of life, clinical case presentations, and the management of CSU and chronic inducible urticaria (CIIndU), including urticaria in special situations such as childhood and pregnancy. This update is a summary of the most current information on urticaria and angioedema and was developed to offer guidance to general practitioners worldwide who must deal with this disease; but is not intended to be a substitute for national and international guidelines that are currently in use.

## **EPIDEMIOLOGY, CLASSIFICATION BASED IN TIME OF EVOLUTION AND TRIGGERING FACTORS. IMPORTANCE OF DISEASE REGISTRIES**

The lifetime prevalence for all types of urticaria is usually described below 10% per different reports, while chronic urticaria (CU) only develops in approximately one-fourth of these individuals.<sup>5,6</sup> Point prevalence of CU, based on coding reports in health systems from different countries, ranges from 0.1 to less than 1% globally.<sup>7-9</sup> Currently the point prevalence is the best method to compare the frequency of CU between different populations but the development of a standardized and practical tool for this purpose remains an unmet need.

From the total of CU patients, one-third suffer from both hives and angioedema, 30%–40% present isolated hives, and around 10% show isolated angioedema.<sup>10,11</sup>

The natural history of the disease has a very wide range. Around half of patients will follow a three-month self-limited evolution and within a year it will resolve in almost 80% of them. However, in more than 10% of patients a duration of 5 years or longer is expected.<sup>12-14</sup> Factors conditioning time to remission will be discussed later.

Females are affected at least twice as often as males, and most patients are over 20 years of age.<sup>1,7,14</sup> In children, the prevalence varies from less than 1% to almost 5%, depending largely upon the methodology.<sup>15-17</sup> Ethnic differences, although described as statistically significant in a wide American population sample, do not seem to deserve in depth attention in real world.<sup>12</sup> Additionally, a proportion of patients experience exacerbations when taking non-steroidal anti-inflammatory drugs (NSAIDs).

The observation that chronic inducible urticaria (CIU) is much more frequent among first-degree relatives of affected individuals than in the general population suggests the existence of a genetic background for the disease and provides clinical support to the reported association between CIU and human leukocyte antigen DR4.<sup>18</sup>

The economic burden of the pathology is not negligible. The CU related cost has been reported to be as high as \$2050 per year per patient in the United States, having a huge personal and familiar impact, particularly in low to middle income countries.<sup>10,19,20</sup> Economic burden analysis using purchasing power parity dollars (PPP\$) demonstrated a higher therapy and inpatients costs in France with almost 3000 \$, compared to less than 1000 \$ in Italy; nonetheless, loss of work productivity was greater in Germany than in France with over PPP\$ 1.000 and over PPP\$ 500.<sup>21</sup>

### **Classification based in time of evolution and triggering factors**

CU is generally classified according to the triggers and the reported signs and symptoms.<sup>6,22,23</sup> While spontaneous urticaria is more frequent, inducible urticaria accounts for approximately

15% of all chronic urticaria patients; however, up to 75% of patients report having both (Table 1).<sup>24-33</sup>

### Importance of disease registries

There has been an evolution in medical care delivery from decision-making based largely upon experience to the use of well documented and validated procedures and interventions which constitutes the backbone of evidence based medicine (EBM).<sup>34</sup> Guideline development is also part of this evolution as guideline panels collect and evaluate published scientific evidence and provide recommendations based upon their overall assessment.<sup>35</sup>

However, registries obtained from real-life patients and databases constitute key instruments for setting health care policies, exploring natural history and endless variables. Additionally registries also provide the background for clinical research. The use of EBM, guideline panels, and patient registries all contribute to providing improved patient care and outcomes.<sup>36</sup>

Registries in allergology have allowed investigators to obtain data inaccessible with other methodologies. Nevertheless, the use of well-designed and executed registries are essential for producing valid outcomes.<sup>36</sup> The use of such registries for CU is invaluable.

An online academia-driven, investigator-initiated registry on chronic urticaria is available from [www.urticaria-registry.com](http://www.urticaria-registry.com). Another registry, the

Latin American Chronic Urticaria Registry, has unraveled the understanding and knowledge of CU in that region.<sup>37,38</sup> The published data of this last registry confirm the classical pattern of age and gender for this population of 300 patients, besides other peculiar data such as low prevalence of parasite associated infestations, and more than half of these patients having significantly affected their quality of life.

Registries provide useful information not only for having an overview of the situation of those patients, but also for specific variables should they represent true elicitors or just innocent co-factors.

## IMMUNOPATHOGENESIS. ENDOTYPES. BIOMARKERS. PREDICTIVE FACTORS

### Endotypes

Urticaria can be divided into 3 clinical phenotypes based on its duration (acute vs chronic) and in the presence or absence of inducing factors (inducible vs spontaneous)<sup>39,40</sup> (Fig. 1). Formerly referred to as chronic idiopathic urticaria, CSU refers to recurrent urticaria lasting more than 6 weeks that occurs in the absence of an identifiable trigger. Although urticaria has always been considered a mast cell-driven disease, it is now known that it involves dysregulation of both mast cell and basophils with their subsequent activation and degranulation as well as the participation of other cells, eg, eosinophils, T and B lymphocytes, epithelial, and endothelial cells.<sup>41</sup>

	Type of Inducible urticaria	Frequency (Percent of total CIU)	References
Physical	Dermographism	2-28.5%	24-26
	Cold Urticaria	2-13.4%	24,26,27
	Heat Urticaria	Unknown	28-30
	Solar Urticaria	<0.4%	31
	Vibratory Urticaria	Unknown	23,30
Non Physical	Delayed Pressure Urticaria	7.3-37%	24,26
	Cholinergic Urticaria	5-11%	26,30
	Aquagenic Urticaria	0,4%	24
	Contact Urticaria	Unknown	23,32

**Table 1.** Prevalence of inducible urticarias

Tissue-resident mast cells can be activated by multiple triggers, immunological or not, highlighting their role in the innate immune response to many skin and mucosal aggressors. Mast cell degranulation can be elicited by the activation of several membrane proteins as a consequence of the crosslinking of allergens recognized by IgE molecules attached to high affinity receptors (FcεRI) on the membrane. There are many other receptors on the mast cell membrane that can also activate it, like C5aR for anaphylotoxins of the complement system (C5a), CRTh2 for PGD<sub>2</sub>, MRGPRX2 for neuropeptides (like substance P), or proteases and cationic proteins (like MBP and ECP), cKit for stem cell factor (SCF), other important cytokine receptors like IL-4Rα and TSLP-R, different kinds of TLRs to recognize PAMPs and DAMPs, and also some inhibitory receptors like Siglec-8 to downregulate the activation pathways.<sup>22</sup> The coagulation pathway has also been implicated with mast cell degranulation through protease-activated receptors (PAR) with thrombin and D-dimer formation. More recently, 2 major mechanisms have been put forward with regards to the pathogenesis of chronic urticaria. The first involves dysregulation of intracellular signaling pathways within mast cells and basophils that lead to defects in trafficking or function of these cells. The second involves the development of IgG autoantibodies to FcεRI or IgE on both mast cells and basophils (autoimmunity type II) or the participation of IgE autoantibodies directed to autoantigens, eg, thyroid peroxidase (TPO), DNA, IL-24 (autoimmunity type I or autoallergy).<sup>42</sup> Histamine

and other mediators, such as platelet-activating factor (PAF), tryptase, leukotrienes, and cytokines released from activated skin mast cells, result in sensory nerve activation, vasodilatation, and plasma extravasation as well as cell recruitment to the urticarial lesions.<sup>22</sup> These multiple ways of mast cell activation and the participation of myriad cells and biomolecules during the process, help us to understand the different endotypes (molecular pathways) that can be seen among the clinical phenotypes discussed above (Fig. 2). A better understanding of these endotypes will help to find relevant molecular targets for biotherapeutic agents (Fig. 3).

### Biomarkers

A biomarker is an objectively measured characteristic that can be used as an indicator of a normal or pathogenic biological process, as well as for pharmacologic responses to a therapeutic intervention. In urticaria, and especially in chronic spontaneous urticaria, a reliable biomarker would be very useful not only to evaluate disease activity, severity, and duration but also to predict response to the treatment. Several potential biomarkers for urticaria have been proposed, but only 5 of them have shown good clinical correlation;<sup>42,43</sup> whereas for other potential biomarkers current evidence is insufficient (Fig. 4):

- Total serum IgE levels
- C-reactive protein (CRP)
- Autologous serum skin test (ASST)

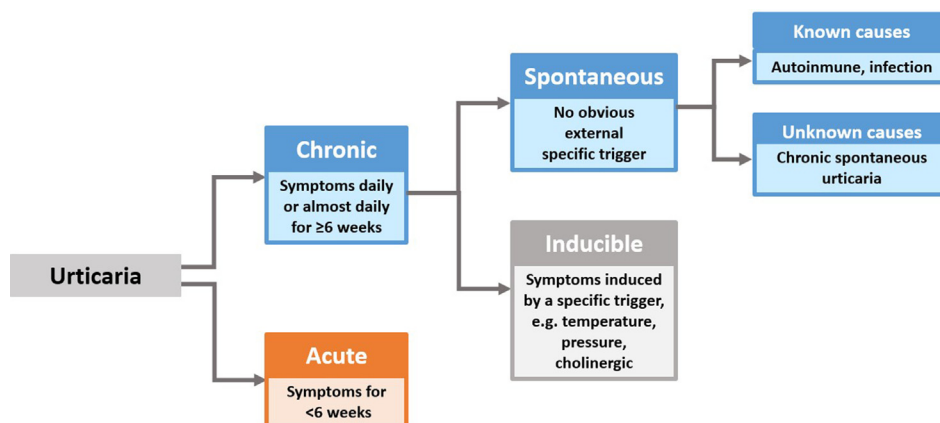
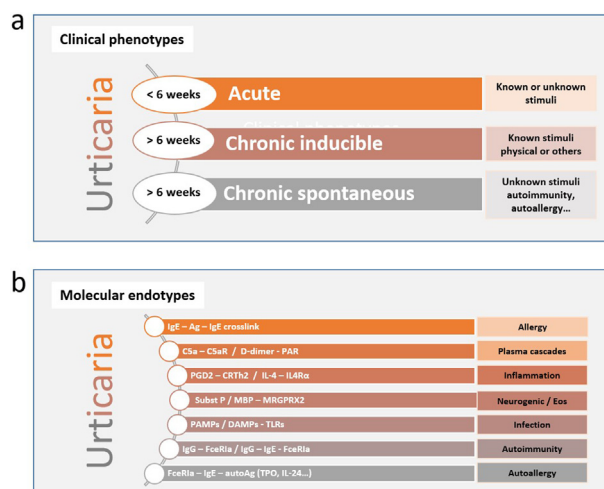


Fig. 1 Urticaria classification



**Fig. 2** Urticaria can be divided into 3 clinical phenotypes on the basis of its duration (less or more than 6 weeks) and in the presence or absence of inducing factors (inducible vs spontaneous). The known stimuli can be a physical agent like temperature, pressure, U/V light, or others as water, chemical irritants or exercise. The unknown stimuli can be related to autoimmunity or autoallergic mechanisms. b. Mast cell activation can be elicited by internal dysregulation and/or external stimuli activation via membrane receptors. Abbreviations. Syk: spleen tyrosine kinase; SHIP = Src homology 2 (SH2)-containing inositol phosphatases; Ag: antigen or allergen (both); C5aR: receptor for C5a; PAR: protease-activated receptor; PGD2: prostaglandin D2; CRTh2: chemoattractant receptor homologous molecule expressed on TH2 cells; IL-4: interleukin 4; IL-4Ra: interleukin 4 receptor alpha chain; Subst P: substance P; MBP: major basic protein; MRGPRX2: mas-related G-protein coupled receptor X2; Eos: eosinophils; PAMPs: pathogen-associated molecular patterns; DAMPs: damage-associated molecular patterns; TLRs: toll-like receptors; FcεR1a: type I Fc epsilon receptor alpha chain; TPO: thyroid peroxidase; IL-24: interleukin-24

- Anti-thyroid peroxidase autoantibodies (IgG *anti*-TPO)

### Predictive factors

Based on the urticaria activity score in 7 days (UAS7), recent studies have analyzed baseline total IgE levels and the response to omalizumab.<sup>44</sup> Unsurprisingly, baseline IgE levels tend to be lower in non-responders, and higher IgE baseline levels predict a better response to omalizumab. Time to relapse was significantly shorter in patients with IgE greater than 100 IU/mL when compared with those who have normal IgE levels.<sup>45</sup>

CRP levels, a sensitive inflammation marker, have shown a good correlation with disease activity and severity. High CRP levels have been associated with increased clinical disease activity

and also with ASST positivity and D-dimer levels, but also with a shorter duration of the disease.<sup>46</sup>

A positive ASST test correlates also with disease severity (attacks > 4 days/week), but no differences have been demonstrated with time to remission. Patients with positive IgG autoantibodies *anti*-TPO had a more prolonged disease when compared with negative *anti*-TPO patients. However, no differences were observed regarding disease severity with the presence of *anti*-TPO.<sup>47</sup>

Finally, inflammatory cytokines can be potential biomarkers for disease severity in CSU. Patients with a severe disease (based on UAS7) had higher IL-17 and IL-33 levels when compared with those with mild disease. Pruritus severity has been also associated with higher levels of IL-31<sup>48</sup> (Fig. 5).

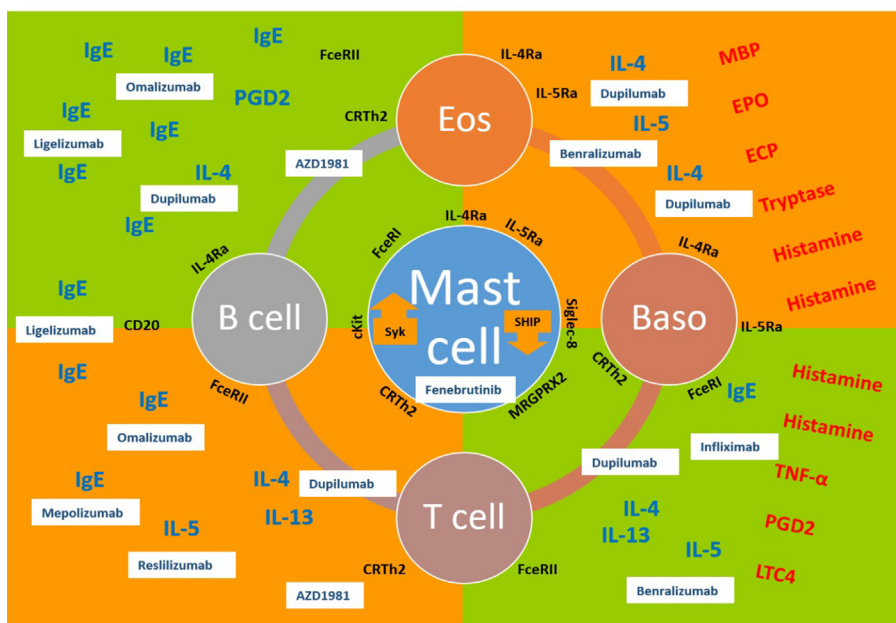
A better understanding of the role of these biomarkers in urticaria may provide the rationale for future new treatment strategies and also for guidance with current conventional treatment.

### Comorbidities of chronic urticaria.

Chronic urticaria (CU) significantly influences the quality of life of patients, which can be negatively impacted by the association with a wide range of comorbidities. CU has been related to a specific pattern of comorbidities including autoimmune, psychiatric, and atopic diseases, all of which are strongly overrepresented among CU patients. However, the pattern is not so clear when malignancies and cardiovascular and gastrointestinal diseases co-exist with CU.

A systematic review of the literature on autoimmune comorbidities to CU showed that the most common autoimmune comorbidities were autoimmune thyroid diseases and vitiligo, and that the most common circulating auto-antibodies were anti-thyroid and anti-nuclear antibodies (ANA).<sup>49,50</sup> In addition, another meta-analysis demonstrated that in systemic lupus erythematosus (SLE) an urticarial rash is common although data for the prevalence of SLE in CU patients does not exist.<sup>51</sup>

It could be speculated that the increased presence of rheumatoid arthritis in CU patients reflects an increased inflammatory status overall, destabilizing mast cells and thereby causing urticaria, whereas in SLE, vitiligo, and thyroiditis the



**Fig. 3** Potential targets for the treatment of chronic urticaria with biotherapeutic agents

pathogenesis is mainly caused by specific auto-antibodies.<sup>49,50</sup>

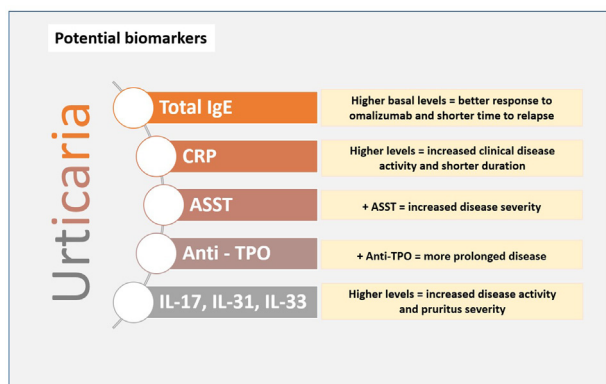
Thyroid disorders have been the diseases most commonly found among CU patients, with the reported prevalence ranging up to more than 50% depending on the inclusion criteria. Association studies using the presence of anti-thyroid antibodies as the criteria usually obtained higher frequencies.<sup>49-51</sup>

In the Scandinavian AWARE-study, a follow up-study of patients with CU refractory to antihistamine treatment, an increased prevalence of atopic diseases including atopic dermatitis, asthma, and rhino-conjunctivitis was demonstrated.<sup>52</sup>

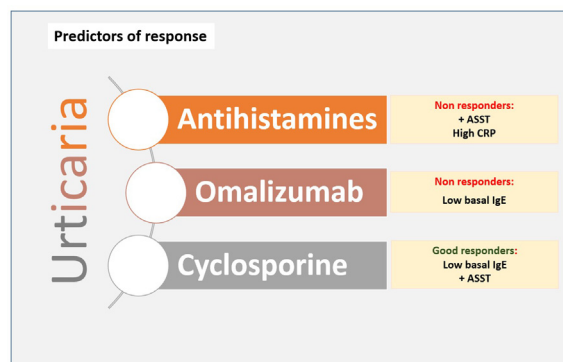
Mastocytosis and anaphylaxis were also significantly associated with CU.<sup>53</sup>

Two large registry studies from Korea and Taiwan demonstrated the same pattern of comorbidities but also an increased prevalence of drug allergies, rheumatic and inflammatory diseases, and cancers as well as psychiatric diseases.<sup>54,55</sup>

In the Taiwan study, the recognition of thyroid disorders was based on the ICD-9-CM classification codes and with the criterion that the study cases must have at least 3 outpatient visit claims with principal/secondary diagnoses of the diseases. The authors found that only 1.78% of the CU patients had thyroid disorders. The lower



**Fig. 4** Potential biomarkers for chronic spontaneous urticaria



**Fig. 5** Biomarkers as predictors of response in chronic spontaneous urticaria

prevalence found could be due to the strict inclusion criteria or different population/ethnic background.<sup>55</sup>

Other studies have found that mental disorders and emotional distress including anxiety, depression, and somatoform disorders were the most common comorbidities identified in CU patients.<sup>56,57</sup>

A few studies have examined the prevalence of cardiovascular diseases but did not find any increased risk of these in CU patients compared to the general population.<sup>58</sup> However, hypertension was previously associated with a more persistent duration of CU.<sup>59</sup>

In a recent nationwide registry study, there was a trend of increasing prevalence of the comorbidities as CU persisted into the second year, but the prevalence of thyroid disorders did not increase steadily as CU persisted longer. In contrast, the prevalence of rheumatic diseases, inflammatory diseases, and psychiatric disorders was higher as CU persisted into the third year. The increased prevalence of these comorbidities in CU patients might reflect a common association of autoimmune-based pathogenesis among CU and rheumatic/thyroid diseases.<sup>56,60</sup>

Several studies have shown a high prevalence of psychiatric comorbidities in CU patients, with the rates ranging up to 60%. Anxiety, depression, and

Most common to least common	Prevalence [references]
Psychiatric diseases <ul style="list-style-type: none"> <li>• Mental disorders</li> <li>• Emotional distress (anxiety, depression and somatoform disorders)</li> </ul>	4.4% - depression <sup>48</sup> 1.0 - psychosis <sup>48</sup> 8.53% <sup>50</sup> 35-65% <sup>50</sup> 31.61% <sup>54</sup>
Atopic diseases <ul style="list-style-type: none"> <li>• Allergic rhinitis, drug or other allergies, or asthma</li> </ul>	2.9% - Rhinoconjunctivitis <sup>48</sup> 2.5% - Atopic dermatitis <sup>48</sup> 4.68x higher in patients with CU <sup>49</sup>
Thyroid disease <ul style="list-style-type: none"> <li>• Hypothyroidism and hyperthyroidism</li> </ul>	0.3% - Thyroiditis <sup>48</sup> 1.9x higher in patients with CU - 12.34% in CU patients and 11.34% in CSU patients <sup>49</sup> 1.78% <sup>50</sup> 12.1%-57.4% <sup>50</sup>
Rheumatic diseases	1.8% - Rheumatoid Arthritis <sup>48</sup> 0.3% - Lupus Erythematosus <sup>48</sup> 0.1% - Vitiligo <sup>48</sup> 2.48% - RA, SLE, AS, PsA/PsO <sup>50</sup>
Inflammatory diseases	9.78% - chronic sinusitis, otitis media, periodontitis, diverticulitis, Helicobacter (H.) pylori infection, peptic ulcer, hepatitis B/hepatitis <sup>50</sup>
Osteoporosis	2.9% <sup>48</sup>
Diabetes mellitus	2.3% <sup>48</sup>
Cancers <ul style="list-style-type: none"> <li>• Stomach, thyroid and liver (most common cancers in CU patients)</li> <li>• Thyroid, liver, and prostate (most common cancers in CSU patients)</li> </ul>	1.37 higher in patients with CU <sup>49</sup>
Hypertension	<sup>48</sup>
Obesity	<sup>48</sup>

Table 2. Prevalence of comorbidities in patients with chronic urticaria

somatoform disorders have been reported to be the most prevalent mental disorders in CU patients, although depression was most prevalent in some studies.<sup>56,60</sup>

The prevalence and future risk of depression was indeed increased, which may reflect that many CU patients have had their diagnosis for years before being referred to a hospital setting. Psychological health, itch, and sleep loss are therefore important parameters in the consultation with CU patients, and perhaps the association between CU on the one hand and depression on the other could be prevented, if the guidelines of the EAACI/GA2LEN/EDF/WAO are adhered to when treating CU patients.<sup>22</sup>

The overall prevalence of any psychiatric comorbidity among CU patients independent of whether studies had a control group was estimated to be 31.6% by Konstantinou et al.<sup>60</sup> The most prevalent psychiatric disorders were found to be sleep-wake disorders (36.7%), followed by anxiety disorders (30.6%), mood disorders (29.4%), trauma and stressor-related disorders (17.3%), somatic symptoms and related disorders (17.2%), obsessive-compulsive and related disorders (9.3%) and substance-related and addictive disorders (4%).<sup>61</sup>

The association of cancer and CU remains controversial. One population-based study reported no association between CU and cancer, and 2 recent studies showed an increased cancer risk in CU patients.<sup>5</sup>

Ghazanfar et al<sup>53</sup> found an increased risk of osteoporosis and diabetes mellitus in CU patients, as both diseases are increased in patients treated with glucocorticoids. Unfortunately, they are still largely used despite the recommendation against their use in current guidelines (EAACI/GA2LEN/EDF/WAO).

The paediatric data on the relation between CU and comorbidities is scarce. In the only available systematic review, Cornillier H et al<sup>61</sup> identified 5 comorbidities and laboratory abnormalities: atopy (6 publications, n = 522 patients), positive autologous serum skin test (ASST; 5 publications, n = 304 patients), autoimmunity laboratory abnormalities (6 publications, n = 391 patients), positive seroprevalence for *Helicobacter pylori* (3

publications, n = 90 patients), 25-OH vitamin D deficiency (2 publications, n = 149 patients), and psychiatric disorders (1 publication, n = 27 patients).

The identified prevalence of atopy was 28.1% in children with CU (15.4% of asthma, 13.8% of allergic rhinitis, and 9.4% of atopic dermatitis).<sup>62</sup> Regarding the link between CU and autoimmunity, the ASST was positive in 36.8% of children with CU; antinuclear antibodies were detected in 10.4% of children, and thyroid antibodies (high titers of antithyroperoxidase and/or antithyroglobulin antibody) in 6.4%. The estimated seroprevalence of *Helicobacter pylori* in children with CSU was 21.1%; 2 patients had suggestive gastrointestinal symptoms associated with chronic urticaria. Vitamin D deficiency, defined by 25-OH vitamin D level <30 ng/mL, was found in 69.1% of children. In only one survey were psychiatric disorders identified in 70.4% (19/27), mainly anxiety disorders (13/27, 48.1%) and disruptive behaviour disorders (7/26, 25.9%).<sup>62</sup>

The prevalence of different comorbidities observed in patients with chronic urticaria is shown in [Table 2](#).

## HEALTH RELATED QUALITY OF LIFE IN CHRONIC URTICARIA

A global assessment of diseases and therapies must include, together with clinical and instrumental parameters, the evaluation of health-related quality of life (HRQoL). Taking into account the patient's perspective allows us to reach a more comprehensive view of the impact of the disease and therapies on daily life.<sup>63</sup> This is particularly important in patients with chronic conditions, when the primary objective of treatment is to reduce the impact of the disease on daily life and to improve subjective well-being.

In this scenario, the role of HRQoL assessment in patients with CSU has been well recognized as critical in detecting the disease burden and the effects of treatments:

- The US Food & Drug Administration<sup>63</sup> and the European Medicines Agency<sup>64</sup> have developed guidances to the healthcare industry on how to include HRQoL in regulatory decision-making.



- The Grading of Recommendations Assessment, Development and Evaluation (GRADE),<sup>65,66</sup> a well defined formal process to rate the quality of clinical evidence and develop evidence-based guidelines, incorporates the patients' perspective as the cornerstone in establishing the strength and direction of recommendations.
- The Global Allergy and Asthma European Network (GA<sup>2</sup>LEN) consensus report has provided recommendations and suggestions for the use of patient-reported outcomes (PROs) including HRQoL both in clinical trials and routine practice for the evaluation of patients with CSU.<sup>67</sup>
- The EAACI/GA2LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of chronic urticaria recommends assessing HRQoL at baseline and at each follow-up visit.<sup>23</sup> Moreover, it emphasizes the relevance of this outcome in guidance of treatment choice.
- the presence of sudden, recurrent and strongly fluctuating symptoms and the debilitating nature of these symptoms<sup>22</sup>
- the occurrence of fatigue, pain, and disrupted sleep, and lack of concentration<sup>68</sup> as common issues, often related to the constant itching that accompanies urticaria
- the visible lesions can lead to embarrassment, shame and difficulties in social life<sup>69,70</sup>
- the presence of psychological complaints such as anxiety, depression, irritability,<sup>3,71</sup> or emotional distress.<sup>22</sup>
- the long disease duration<sup>22</sup>
- the difficulty to identify the causes and/or the triggers<sup>22</sup>
- the unsatisfactory response to the currently available treatments<sup>22</sup>

While CSU is not a life-threatening condition, it deeply interferes with HRQoL.<sup>6</sup> The reason for this impact depends on several aspects that characterize the disease:

The knowledge about HRQoL in people with CSU has been obtained during the last 20 years. The availability of validated questionnaires, both generic and speciality-specific, and the development of new specific tools for CSU, allowed exploration of how the disease impacts patient's experience<sup>72-76</sup> (Table 3).

	Skin specific	Disease specific	CSU with wheals and angioedema	CSU with angioedema alone	Recommended by EAACI/GA2LEN/EDF/WAO guideline	Minimal Important Difference (MID)
Dermatology Life Quality Index (DLQI)	X		X	X		X
SKINDEX-29	X					
Chronic Urticaria Quality of life Questionnaire (CU-Q2oL)		X	X	X	X	X
Chronic Urticaria Patient Perspective (CUPP)		X	X	X		X
Angioedema Quality of Life Questionnaire (AE-QoL)		X	X	X	X	X

**Table 3.** Validated questionnaires for the assessment of HRQoL in CSU

The use of generic questionnaires - tools that allow investigators to make comparisons between different health conditions - has shown that, from a subjective viewpoint, CSU represents a major burden. Patients treated for CSU, compared to matched controls, had significantly worse scores in both the Physical and Mental Component of health status.<sup>77</sup> The HRQoL impairment does not depend on age, sex, disease duration, or the presence/absence of angioedema.<sup>3</sup> The comparison with other chronic diseases further highlights the quality of life impairment with CSU. The effects of CSU on HRQoL were similar to those of coronary artery disease.<sup>78</sup> Moreover, CSU patients have significantly worse physical functioning, pain perception, and perceived health than patients with respiratory allergy<sup>2</sup> and a more marked impairment in social functioning than those with type 1 diabetes mellitus.<sup>79</sup>

The use of skin-specific questionnaires (that allow the comparison of dermatological diseases) and, even more, of disease-specific tools has allowed a better determination of the qualitative characteristics of HRQoL in CSU patients. Large or extremely large effect on HRQoL is a common feature<sup>80-82</sup> and the HRQoL impact increases with the severity of the disease.<sup>83</sup> Moreover, changes in signs and symptoms are strictly related to changes in HRQoL scores.<sup>84</sup> Patients with angioedema reported statistically significantly worse HRQoL than those without angioedema.<sup>85</sup>

Research activities using specific HRQoL questionnaires, have allowed investigators to capture the subjective experience of CSU patients in all its dimensions: symptoms, impact on life activities, sleep, limits, looks,<sup>85</sup> functioning, fatigue/mood, fears/shame, and food.<sup>76</sup> The EAACI/GA2LEN/EDF/WAO guidelines recommended the use of chronic urticaria quality of life questionnaire (CU-Q2oL)<sup>1</sup> and angioedema quality of life questionnaire (AE-QoL)<sup>76</sup> for assessing and monitoring HRQoL in CSU patients. Both tools have been validated and used in clinical research. On the contrary, the chronic urticaria patient perspective (CUPP)<sup>75</sup> constitutes a user-friendly tool to assess HRQoL in patients with CU in daily practice. It owns all the characteristics that are required for use with individual patients. The minimal important difference (MID), defined as the smallest difference in a score for an outcome of

interest that patients perceive as important, and which would lead to the consideration of a change in the management,<sup>86</sup> has been determined for CU-Q2oL, AE-QoL and CUPP.<sup>87</sup> MID is crucial to interpreted HRQoL changes of measurement scores and to implement HRQoL assessment in routine practice.

The effect of available treatments on HRQoL of CSU patients has been evaluated in 24 clinical trials.<sup>88-100</sup> Although the studies are different with regards to methodology, population, therapy, and questionnaire, the results indicate a HRQoL improvement after treatment.

In view of a patient centered medicine, available knowledge and continuing experience with the assessment of HRQoL allow researchers and clinicians to better understand, monitor, and manage CSU.

## CLINICAL CASES: CHRONIC SPONTANEOUS URTICARIA (CSU), WITH OR WITHOUT ANGIOEDEMA

Chronic spontaneous urticaria (CSU) presents with urticaria only in approximately 40% of patients, with angioedema in 40%, and as isolated angioedema in up to 20% of cases. The latter presentation must differentiate between histaminergic and non-histaminergic angioedema conditions using well established algorithms that are available for physicians to follow (Fig. S1 in supplementary materials).<sup>22</sup> When a patient presents with CSU, it is essential to get a thorough history that should query for duration, evanescence, and severity which can be quantified in terms of number of hives over the entire body and severity of itch. Underlying contributing factors such as foods, medications, thyroid disease, autoimmune disorders, chronic infections, and, rarely, malignancies as well as concomitant inducible hives including dermatographism, cold, heat, exercise, delayed pressure, and cholinergic should be determined. In addition, previous response to treatments prescribed is often useful for determining where to begin in the treatment algorithm. Validated instruments are now available that can accurately quantify CSU with or without angioedema severity and assess control and quality of life that are recommended for initial assessment and at

each subsequent visit to determine treatment response. Guidelines recommend limiting diagnostic testing unless the history provides clues to an underlying cause.<sup>22</sup> Patients must be educated that CSU is due to an internal mechanistic problem resulting in abnormal mast cell and/or basophil activation, rather than an external cause such as allergen or food sensitizations, and that skin or serologic testing to aeroallergens or foods is usually inappropriate unless the history suggests concomitant allergic rhinitis/asthma or food allergy. International and national evidence-based treatment algorithms provide guidance for the clinician for selecting therapies based on the severity of the patient's presentation. There are some distinct differences between international and US guidelines that clinicians should be familiar with, which are summarized in Fig. S2 in supplementary materials. When patients are not responsive to initial therapy with H1-antihistamines, even at doses four times FDA/EMA recommendations, treatment should be advanced to Step 3 therapy with omalizumab, a monoclonal IgG *anti*-IgE antibody, which has been found to be very effective in up to 45% of H1-antihistamine unresponsive CSU. When patients are unresponsive to omalizumab, options become more limited to Step 4 therapy with immunosuppressants such as cyclosporin, or other anti-inflammatory medications, the latter which are listed in an "Alternative treatment" category in the international guidelines.<sup>22</sup> The following two cases illustrate the evaluation and management of CSU with and without angioedema.

### Case #1: CSU with angioedema

A 33 year-old female presents with history of CSU since 2013 which resolved in 2017 but recurred in the last 6 weeks. The hives are described as being evanescent and very severe involving over 90% of her body with an itch severity score of 10 on a scale 1-10. An urticaria activity score summed up over 7 days (UAS7) which measures the number of hives over the entire body (0-3 scale) and itch intensity (0-3 scale) with a maximum weekly score of 40 was "40". The patient has not slept and has experienced absenteeism and presenteeism at work over the past few weeks. She endorses daily lip and tongue swelling associated with urticaria and some throat

discomfort with coughing secondary to difficulty in swallowing secretions due to her enlarged tongue. In addition she noted lumps on the bottoms of her feet. The hives were so pruritic that they hurt and were associated with intermittent arthralgias and chills. She has been to the urgent care center on 2 different occasions, once 3 days before her visit, where each time she was treated with a brief course of glucocorticoids and diphenhydramine which helped to reduce the severity of the hives and swelling, but each time she came off the medications they became significantly worse again. She denied any relationship to prescription or over the counter medications or foods. She had no history of thyroid disease, autoimmune disease, or chronic infections. There was no family history of CSU or angioedema. She noted worsening of the hives at pressure points and with cold temperatures. She works as an x-ray tech and is currently nursing an 8-month-old child.

Physical examination revealed a well-developed, well-nourished female in significant distress due to the severity of her hives. Her blood pressure, pulse, and respiratory rate were normal. A UAS score during her visit was "40" and an urticaria control test score (UCT) was 0 (scale 0-16, with 0 being totally uncontrolled). The hives were raised and erythematous with a bluish hue and serpiginous borders that coalesced. Her lower lip was slightly swollen. There was no lymphadenopathy, nor organomegaly, and her respiratory and cardiovascular examination was normal. Her skin did not urticate when stroked with a dermatographometer device. A temperature test was negative for cold induced urticaria.

At the time of her visit she had been taking 60 mg of prednisone for 3 days prescribed by the urgent care physician and was still not controlled. Given the chronicity, the visual appearance of the hives and systemic symptoms along with her poor response to oral glucocorticoids, a sedimentation rate, C-reactive protein, complete blood count with differential, thyroid stimulating hormone, autoantibodies to thyroid peroxidase, total IgE, chronic urticaria index, C3, C4, ANA, rheumatoid factor, glucose-6-phosphate dehydrogenase level and a skin biopsy were obtained to identify an underlying vasculitis or autoimmune condition and to obtain biomarkers useful for determining best therapeutic options if conventional therapy with

H1-antihistamines was not effective. The patient was instructed to taper the prednisone slowly by 5 mg every 2 days and to start cetirizine 20 mg twice a day, and montelukast 10 mg a day. The latter two treatments which are not primary recommendations in the international guidelines but recommended as Step 2 therapy for the Joint Task Force United States Urticaria guidelines, were started due to their safety, low cost, and the severity of the patients' hives. She was seen one week later to review the biopsy results and remove the suture. She was still tapering the prednisone, and the hives were now intermittent with a UAS7 of 16 and UCT 10. The biopsy showed perivascular lymphocytes with eosinophils but no evidence of vasculitis. Her laboratory tests revealed a CRP 17.87 (normal  $\leq 6$ ), and normal thyroid function, a slight increase in WBC of 11.7 ( $3.7\text{--}10.3 \times 10^3/\text{mol}$ ), slight increase in peripheral neutrophils of  $8.9 \times 10^3/\text{mol}$  (normal  $1.6\text{--}6.1 \times 10^3/\text{mol}$ ) and a low IgE of 12 kU/L (normal  $\leq 240\text{kU/L}$ ) (despite the low IgE levels (12 kU/L) this patient responded brilliantly to omalizumab). She was instructed to continue tapering the prednisone, continue the current Histamine-1/Histamine-2 antagonists and leukotriene modifying agent medication combination, and return in 4 weeks for further assessment. A free T4 and T3 level were ordered to assess for hyperthyroidism and her CRP was repeated. Paperwork for omalizumab insurance authorization was completed in case she required advancement to Step 3 therapy.

Upon return 4 weeks later she was off prednisone; the hives were improved, but she still reported a UCT score of 7 and a UAS7 score of 18. A free T3 and T4 were normal and her CRP was now normal. Omalizumab 300 mg was approved, and the first injection was administered subcutaneously during her visit. She returned 4 weeks later for follow-up and her second injection. She reported now that her UCT score was 16 and her UAS7 score was 4 and was feeling much better overall all without any side effects from the medication. During her third injection one month later she reported a UCT of 16 and a UAS7 = 0.

**Discussion:** This case represents a severe case of hives with angioedema that was associated with features suggesting an underlying systemic process given the nature of the hive presentation and associated systemic symptoms. The patient was

already on prednisone which was continued at a slower taper to provide better control and more comfort while Step 2 therapy was initiated. Testing was performed strictly to investigate clinical suspicions for an underlying vasculitis or systemic condition. In fact, the CRP was increased and the screening TSH was low however further testing failed to reveal evidence of hyperthyroidism. Despite prednisone and Step 2 therapy she was not well controlled, so she was advanced to Step 3 treatment with omalizumab. In preparation for initiating this therapy, the patient was screened with a total IgE as low levels have been associated with slower or poorer response. In addition, the patient was evaluated for the biomarkers TPO and a CU-index, a marker for high affinity IgG anti-FcER1 alpha subunit antibodies that if positive are also predictive of poorer responses to omalizumab. In this patient, these tests were negative and the patient subsequently demonstrated an excellent and rapid response to omalizumab. Of note, she had associated angioedema with the urticaria which was also controlled with omalizumab as has been shown in post-hoc analysis of data from clinical trials. An additional nuance of this case was that the patient was breast feeding while being treated with high dose antihistamines and omalizumab. Although there are no controlled studies demonstrating safety of these agents in pregnant and lactating women, the international guidelines support using these therapies in these special populations based on long-term clinical experience and safety registries.<sup>22</sup> In addition, using the validated patient reported outcomes instruments was very helpful for determining control and directing treatment decisions.

### Case #2: CSU without angioedema

A 26-year-old female presents with CSU since 2017 when she started to experience spontaneous hives over different parts of her body mostly on her arms, legs and hip. Her UCT score was 8 and UAS7 was 20, but the itch intensity was much lower than the number of hives. There were no inducible triggers for the hives. Her primary care physician had recently prescribed a course of prednisone in conjunction with diphenhydramine, the latter which she was using as needed; however, the hives and swelling recurred when she was off medications. In addition to diphenhydramine which made

her tired, she was also prescribed montelukast. Unfortunately she experienced vivid nightmares, and this medication was discontinued. She works as an administrative assistant and noted the medications were interfering with her work performance. She had some previous blood tests including a CBC with differential and TSH which were normal. There was no relationship of the CSU to medications or foods. She had seen another allergist who tested her to aeroallergens and foods which were reportedly negative. During her current visit the physical examination showed scattered erythematous wheals with serpiginous borders over her arms. No angioedema was observed. Otherwise there were no other relevant findings on physical exam.

Based on the chronicity of her CSU and responsiveness to H1-antihistamines, she was started on fexofenadine 180 mg twice a day and scheduled a follow-up visit in 4 weeks. No additional testing was performed. She returned 4 weeks later and had a UCT of 16 and a UAS7 = 0. She was tolerating the medication without side effects, and her quality of life was much improved. She was instructed to continue the medication and return in 3-4 months. At her third visit, her hives were still controlled and the fexofenadine was reduced to once a day.

**Discussion:** This is a relatively straight forward case of CSU that was not initially evaluated or treated appropriately. She was being treated with a first generation H1-antagonist that was making her tired and affecting her work. Furthermore, she was seen by another allergist who performed skin testing to aeroallergens and foods when there was no history of allergic rhinitis, asthma, or food allergies.<sup>22</sup> She was started on fexofenadine at 2 times the recommended FDA dose (Step 2 therapy) which was very effective at preventing recurrent hives. This regimen was continued until it was clear she was not having breakthrough hives (UAS7 = 0) at which point the dose was decreased to once a day. She noted her leisure and work quality of life had significantly improved after starting this medication regimen.

#### *Takeaway Points:*

- 1) Guidelines are useful for guiding clinicians in the appropriate evaluation and management of CSU patients.

- 2) CSU is rarely caused by external causes.
- 3) Validated patient reported outcome instruments are valuable for assessing disease severity and monitoring response to treatment.
- 4) Excessive testing including skin testing to aeroallergens or foods, is not recommended unless the history suggests otherwise.
- 5) High dose H1-antagonists control over 40% of CSU patients.
- 6) Patients with and without angioedema and hives respond to omalizumab.

## THERAPEUTICS AND INTEGRAL MANAGEMENT OF CSU AND CINDU

### General measures

Patient interrogation and physical examination may disclose environmental symptom triggering or aggravating factors of chronic urticaria (CU). When identified, it is mandatory to avoid or reduce the exposure to such factors (physical, drugs: NSAIDs, ACE inhibitors, foods, other allergens, contactants, emotional stress). Treatment of concomitant infections, such as *H. pylori*, as well as urinary tract, parasites, dental, or gynecological infections is also pertinent.<sup>22</sup> Other comorbid conditions such as autoimmune thyroid disease, hypertension, and metabolic syndrome should be treated.<sup>11</sup>

Up to 40% of patients with chronic spontaneous urticaria (CSU) experience exacerbations when exposed to aspirin and NSAIDs. Ten to fifty percent of patients with CSU also have associated inducible urticaria. In consequence, treatment of comorbid inducible urticaria is necessary.<sup>11</sup>

Additional measures that contribute to decrease pruritus, the most disturbing symptom of CU, and patient discomfort are the application of physical measures, for example cold compresses (not in patients with cold-induced urticaria).

## CONCLUDING REMARKS

The prevalence of chronic urticaria in the population has been estimated to be between 0.1% and 1.0%. Quality of life of affected patients may be severely compromised, and the costs of the

disease for the health system can be substantial. In recent years there have been remarkable advances in the understanding of the pathophysiology of urticaria that have prompted investigators to explore new medications, especially biologics, for patients with severe refractory urticaria. Multiple cell types are involved in the production of symptoms, mainly mast cells, basophils, eosinophils, T and B lymphocytes, and epithelial and endothelial cells. It is proposed that dysregulation of intracellular signaling pathways and autoimmune phenomena play a major role in mast cell/basophil activation leading to inflammatory mediator release in the skin resulting in wheals and angioedema.

Patients may complain of wheals (about 40%), angioedema (40%), or both (20%), whereas no identifiable trigger factors for the symptoms are present in a large proportion of affected subjects (chronic spontaneous urticaria), although in some of them external factors, mainly physical, could be suspected and proven (chronic inducible urticaria). It is also pertinent to mention that some patients may show a combined pattern of spontaneous and inducible urticaria.

Currently biomarkers for the prognosis of CU and therapeutic response to different therapies have been identified which are useful for routine management. Finally, we recommend that clinicians follow the guidelines, utilize validated PRO instruments, and use medications with proven efficacy and safety. In the near future new biologics and small molecules that are currently under investigation will be incorporated into the treatment of severe and refractory CU.

#### Abbreviations

ACE, angiotensin converting enzyme; AE, angioedema; AE-QoL, angioedema quality of life; ASST, autologous serum skin test; C5a, complement C5a; C5aR, complement C5a receptor; CRP, C reactive protein; CRTh2, chemo-attractant receptor-homologous molecule expressed on T helper type 2 cells; CIndU, chronic inducible urticaria; CsA, cyclosporine A; CSU, chronic spontaneous urticaria; CU, chronic urticaria; CUPP, Chronic Urticaria Patient Perspective; CU-Q2oL, chronic urticaria quality of life; DAMPs, damage-associated molecular patterns; DLQI, dermatology quality index; DNA, desoxyribonucleic acid; EBM, evidence-based medicine; ECP, eosinophil cationic protein; FcεRI, high affinity IgE receptor I; GA2 LEN, Global Allergy and Asthma European Network; GRADE, Grading of Recommendations Assessment, Development and

Evaluation; EAACI, European Academy of Allergy and Clinical Immunology; EDF, European Dermatology Foundation; HR4, histamine receptor 4; HRQoL, health-related quality of life; IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M; IL-1, interleukin-1; IL-2, interleukin-2; IL-2R, interleukin-2 receptor; IL-3, interleukin-3; IL-4, interleukin-4; IL-5, interleukin-5; IL-17, interleukin-17; IL-24, interleukin-24; IL-31, interleukin-31; IL-33, interleukin-33; IL-4Rα, Interleukin-4 receptor alpha chain; IU, inducible urticari; MBP, major basic protein; MRGPRX2, Mas-related G protein-coupled receptor X2; NSAIDs, nonsteroidal anti-inflammatory drugs; NS AHs, non-sedating antihistamines; OMA, omalizumab; PAF, platelet activating factor; AMPs, pathogen-associated molecular patterns; PAR, protease-activated receptors; PGD2, prostaglandin 2; PPP\$, power parity dollars; PIDs, Primary immunodeficiency diseases; PROs, patient-reported outcome; SCF, stem cell factor; TNF-α, tumor necrosis factor alpha; TLR, toll-like receptor; TSLP-R, thymic stromal lymphopoietin receptor; UAS-7, urticaria activity score-7; UV-A, ultraviolet light-A; UV-B, ultraviolet light-B; WAO, World Allergy Organization.

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#### Author contributions

Mario Sánchez-Borges: Designed the outline of the paper. Wrote the section on Management.

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Jose Antonio Ortega Martell: Wrote the section on Immunopathogenesis.

Ilaria Baiardini and Walter Canonica: Wrote the section on Quality of Life.

Mario Morais de Almeida: Wrote the section on Comorbidities.

Jonathan Bernstein: Wrote the section on Clinical cases: Chronic spontaneous urticaria (CSU), with or without Angioedema.

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### Appendix A. Supplementary data

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