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**Abstract**

Chronic urticaria (CU), affects about 1% of the world population of all ages, mostly young/middle-aged females, usually lasts for several years (>1 year in 25-75% of patients), and often takes >1 year before effective management is implemented. It presents as chronic spontaneous urticaria (CSU), chronic inducible urticaria (CIndu) or both in the same person. More than 25% of cases are resistant to H<sub>1</sub>-antihistamines, even at higher doses, and 3<sup>rd</sup> and 4<sup>th</sup> line therapy (omalizumab and ciclosporin) control the disease only in two thirds of H<sub>1</sub>-antihistamine resistant patients.

Here, we review the impact of CU on different aspects of patients' QoL and the burden of this chronic disease for the patient and the society.

CU may have a strong impact on health-related quality of life (HRQoL), particularly when CSU is associated with angioedema and/or CIndU (DLQI>10 in 30% of patients). Comorbidities, such as anxiety and depression, that are present in more than 30% of CSU patients compound HRQoL impairment. Severe pruritus and the unpredictable occurrence of wheals and angioedema are responsible for sleep disorders, sexual dysfunction, limitations on daily life, work and sports activities, interfering with life within the family and in society and with patients' performance at school and work (6% absenteeism and 25% presenteeism). Apart from treatment costs, with annual values between 900-2.400 PPP\$ (purchasing power parity dollars) in Europe and US, CU is associated with a high consumption of medical resources and other indirect costs, which may reach a total annual cost of 15.550 PPP\$.

**Key words:** Chronic urticaria, chronic spontaneous urticaria, chronic inducible urticaria, quality of life, global burden, costs, angioedema, comorbidities, review.

## Introduction

Chronic urticaria (CU) is defined by the occurrence of wheals (hives), angioedema or both for more than 6 weeks, with lesions occurring either spontaneously (chronic spontaneous urticaria – CSU) or in response to definite and reproducible triggers like friction, cold, heat, solar radiation, pressure, or exercise (chronic inducible urticaria - CIndU).<sup>1</sup> Autoimmunity type I (autoallergy with IgE autoantibodies to IL-24, thyreoperoxidase, double-stranded DNA, and other autoallergens) or type IIb (IgG antibodies to the patient's own IgE or its high affinity receptor - FcεRI) are considered to be pathogenic in many patients with CSU,<sup>2</sup> but other mechanisms of mast cell activation and modulation<sup>3</sup> and other elicitors, like nonsteroidal anti-inflammatory drugs (NSAIDs), are also involved.<sup>1</sup>

CU is a common disease worldwide<sup>4</sup> that affects all ages. CU has a variable duration but can last for several years.<sup>5</sup> CU has a significant impact on health-related quality of life (HRQoL),<sup>6</sup> similar or greater than moderate-to-severe psoriasis,<sup>7</sup> atopic dermatitis, asthma, and severe coronary artery disease requiring bypass grafting.<sup>6,8,9,10,11</sup> In addition, CU significantly affects performance at school and work and is associated with a high consumption of medical resources, high treatment costs and other direct and indirect costs to society.<sup>12,13</sup> Because CU carries a significant humanistic and economic burden,<sup>14</sup> this review will discuss the spectrum of detrimental consequences that CU has on patients, health care systems and societies on a global scale (Fig. 1),(Table1).

The authors worked in groups of three to review the literature considered relevant for each of the sections, and the leading authors (MG, AGA and MM) composed the final document that was further reviewed and approved by all the authors.

## The prevalence of CU in the world is high and increasing

CU is common in every country globally, and its prevalence has increased 2 to 10 fold over the last decade.<sup>4,15,16,17</sup> A recent systematic review and meta-analysis reported an overall lifetime CU prevalence of 4.4% and an overall point prevalence of 0.7%, ranging from 0.1% in North America to 0.5% in Europe and up to 1.4% and 1.5% in Latin America and Asian countries, respectively.<sup>18</sup> Prevalence data from Africa is lacking, but all ethnicities appear to be affected, although prevalence may vary in different populations either due to genetics or life-style habits (Fig.2).

CU affects mainly young to middle-aged adults,<sup>13</sup> with a mean age of onset in patients in their late twenties to forties.<sup>18,19,20,21</sup> However, recent studies suggest that children and elderly populations are affected to a similar extent. A prevalence of 1.4% was reported for CU in under 18 year olds,<sup>22</sup> and 1% for children under 14 years.<sup>23</sup> Data on elderly patients is largely lacking, but patients aged  $\geq 65$  years represent 10%-21.7% of CU cases.<sup>24,25</sup>

CU, and especially CSU, is more common in women (up to 80%)<sup>12,18,19,20,25</sup> but this gender difference is not apparent in children under 15 years<sup>4,23</sup> nor in the elderly,<sup>24</sup> and is also less evident in Asian populations.<sup>4</sup>

The real prevalence of CSU with isolated angioedema (without wheals) is not known but considered to account for about 10% of all CSU cases.<sup>26,27</sup> It is less common than its presentation with angioedema and wheals together and wheals alone. In patients with recurrent angioedema without wheals, hereditary variants, i.e. hereditary angioedema, and other forms of bradykinin-mediated angioedema, e.g. angiotensin converting enzyme (ACE)-inhibitor induced angioedema, need to be ruled out, by history-taking and appropriate follow-up diagnostics.<sup>1</sup>

The prevalence of different CIndUs is not known. Concomitant CIndU occurs in 7 % to 30% of adult CSU patients.<sup>28,29,30</sup> Patients may suffer from more than one type of CIndU and, amongst patients with CIndU, 14% are also reported to have CSU.<sup>29</sup> The most common type of CIndU is symptomatic dermographism followed by cold urticaria and delayed pressure urticaria.<sup>28,29</sup> The median age at onset of CIndU symptoms is 40 years,<sup>30</sup> but up to 22% of children with CU also have CIndU, either CIndU alone or, in a quarter of them, associated with CSU.<sup>31</sup>

### **CU patients face long delays in diagnosis and treatment**

The diagnosis of CSU is relatively easy to make. A simple set of clinical and laboratory investigations exclude urticaria mimickers, such as urticarial vasculitis and auto-inflammatory syndromes in patients with urticarial wheals as well as bradykinin-mediated angioedema in patients with isolated swellings.<sup>1,32</sup> Unexpectedly, the time from CU onset to proper diagnosis and correct management is usually long, with considerable variability across countries. The mean time to diagnosis reported for Canada was 24 months,<sup>12</sup> for Central/South America 3 years and for Western Europe 2-4 years.<sup>19</sup> In the US, it takes more than 6 weeks to see a physician or consult with a specialist in about 45% of CU patients,<sup>33</sup> whereas in Japan 85% of patients consulted an allergist or dermatologist within one month from the onset of urticaria.<sup>34</sup>

After a correct diagnosis, many patients repeatedly undergo unnecessary testing to identify a cause, often due to misperceptions by the patient and/or physicians that CU is due to type I allergy,<sup>18,33,35</sup> (i.e., food allergy). This leads to significant frustration in up to 67% of patients,<sup>36</sup> not to mention the high consumption of medical resources with no additional benefit.<sup>37</sup> Also, as physicians are frequently unaware of urticaria guidelines,<sup>38</sup> they give misinformation concerning the risk of anaphylaxis and recommend, inappropriately, first generation sedating anti-histamines, on-demand treatment only or the prolonged use of systemic corticosteroids.<sup>13,18,20</sup> As a consequence, many patients get frustrated and stop seeking treatment, and surveys indicate that more than 50% are not under the care of a physician.<sup>18</sup>

### **CU is a disease of long duration**

CU is considered a self-limiting disease although it has a long duration and may recur over time. Among adults the average duration of CSU is estimated to be 11.5±10.8 years,<sup>18</sup> with remission occurring within 1 year after onset only in 20-75%<sup>27,39</sup> and within 5 years in only 30-55%.<sup>10,40,41</sup>

Clinical predictors of longer duration include insufficient response to a standard-dosed antihistamine (51% and 66% persistence, respectively, at 2 and 5 years),<sup>42</sup> late onset

(>45 years),<sup>43</sup> concomitant CIndU,<sup>43</sup> intolerance to NSAIDs,<sup>44</sup> and a relapsing course,<sup>40,43</sup> defined as CU recurring at least 6 months after symptom resolution and cessation of controller therapy.<sup>45,46</sup> Some laboratory biomarkers (high C-reactive protein and D-dimers) may predict disease severity<sup>47</sup> but are not related to disease duration. Autoantibodies to FcεRI and a positive autologous serum skin test (ASST) or basophil activation test/basophil histamine releasing assay (BAT/BHRA) are related to autoimmune type IIb CSU, but are not by themselves associated with a longer disease duration in most studies.<sup>2</sup>

CIndU is reported to have a lower resolution rate compared to CSU,<sup>40</sup> with only 13% and 50% of CIndU patients becoming free of symptoms, respectively, within 1 year and 5 years.<sup>29</sup> For example, solar urticaria can persist over 5 years in >50% of patients,<sup>48</sup> and cold urticaria is still present in >25% of patients after 10 years.<sup>49</sup>

The resolution rate of CU in children is also low with studies reporting a 10% resolution rate per year in Canada<sup>31</sup> and remission rates in Asia of 19%, 54%, and 68%, respectively at 1, 3, and 5 years.<sup>50</sup> Data on disease duration in the elderly are lacking. The published information on disease duration may be biased, as many studies reported Kaplan-Meier curves for patients who still had CU at the time of assessment,<sup>41,45,51</sup> and many calculations on disease duration consider the first consultation as the disease start, which is not reflective of the true CU onset.

### **CU is often resistant to standard treatment**

On average, only 50% of CSU patients have an adequate response to non-sedating antihistamines (nsAH) at standard or up to fourfold doses,<sup>52,53,54</sup> and this percentage is even lower when angioedema is also present.<sup>55</sup> However, response rates do vary greatly across studies. A recent observational study demonstrated very low rates of disease control with a standard-dosed nsAHs (18%), but favourable outcomes with higher doses in 74% of subjects.<sup>55</sup> In a systematic review, 60% of patients were unresponsive to standard-dosed nsAHs, and up dosing controlled pruritus but not the number of wheals.<sup>5</sup> Up to 1 in 4 patients require treatment with omalizumab or ciclosporin, respectively, the 3<sup>rd</sup> and 4<sup>th</sup> line therapies, according to the EAACI/GA<sup>2</sup>LEN/EDF/WAO urticaria guideline.<sup>1</sup> Patients with type I autoimmune (autoallergic) CSU, who usually have high normal or elevated IgE levels, tend to respond fast and well to omalizumab therapy.<sup>56,57,58</sup> In contrast, patients with type IIb autoimmune CSU, who have a positive ASST and BHRA/BAT, more often exhibit basopenia and eosinopenia, often with a low or very low serum IgE, show a slow and poorer response to omalizumab<sup>2,56</sup> but a good treatment outcome with ciclosporin.<sup>59,60</sup>

Although there are fewer studies in children, resistance to H<sub>1</sub>-antihistamines also occurs, even after up dosing,<sup>61,62</sup> and management should follow the recommendations for adults, adjusted for age and weight.<sup>1</sup>

### **The impact of angioedema**

There is some variation on the numbers of patients with CSU experiencing both hives and angioedema or angioedema alone. Angioedema is reported in approximately 40% to 60% of patients with CU,<sup>20,21,19,63</sup> but angioedema may be underdiagnosed, with

patients reporting it more often than their physicians (65.8% versus 41%).<sup>26,64</sup> The average intensity of angioedema during the previous 6 months was rated as severe, moderate, mild, and negligible by 31%, 46%, 20%, and 2% of patients, respectively.<sup>64</sup> Compared to CSU with wheals alone, the occurrence of angioedema is associated with a prolonged disease duration (persistent symptoms at 1 year in 43–48% vs 64–70%),<sup>27</sup> a more severe disease,<sup>26</sup> poorer response to antihistamines,<sup>65,66</sup> and worse HRQoL.<sup>26</sup>

### **CU comes with high QoL impairment**

#### *HRQoL impairment in chronic spontaneous urticaria*

HRQoL is substantially affected in CSU patients.<sup>27</sup> Among other skin disorders, CSU is among those with the highest HRQoL impairment,<sup>6,78</sup> with DLQI>10 in >30% of patients referred to urticaria clinics.<sup>13,19,20</sup> The main factors responsible for the physical, social, and emotional impact of CSU include the sudden and unpredictable appearance of wheals and angioedema,<sup>67</sup> and itch, which is very distressing and has a major impact on sleep and patients' well-being.<sup>68,69</sup> Many CSU patients have daily or almost-daily signs and symptoms<sup>67</sup>, which often occur during the evening, night time, or early morning,<sup>70</sup> but their exact timing and location, duration, and severity can change considerably from day to day.<sup>67</sup> Accordingly, CSU-affected patients live in a constant expectation of newly appearing wheals and angioedema,<sup>10</sup> including the fear of suffocation,<sup>71</sup> and many patients have a feeling of losing control over their lives.<sup>10</sup> Further negative emotions include self-consciousness and embarrassment,<sup>10</sup> frustration,<sup>10</sup> feeling sad and discouraged,<sup>7,72</sup> being tired and irritable,<sup>10</sup> weak,<sup>10</sup> and anxious.<sup>7,10,73,12</sup> This is often further exacerbated by underestimation of the disease burden by others, including treating physicians.<sup>73,26</sup> CSU leads to an impairment of sleep and cognitive functions,<sup>7,10,70,12,74</sup> and has a major impact on social interactions,<sup>9</sup> work performance,<sup>7,12</sup> daily life functioning,<sup>10,12,79</sup> including interpersonal relationships and sex life.<sup>10,75</sup>

HRQoL impairment correlates generally with disease activity,<sup>12,76,77</sup> however there must be additional influencing factors as correlation with the urticaria activity score for 7 days (UAS7) is not high.<sup>76,77,78</sup> Age and gender have an impact on some dimensions of HRQoL,<sup>79,80</sup> but a major driver are psychiatric comorbidities, such as anxiety and depression, which induce a stronger HRQoL impairment.<sup>81,82,83,84,85</sup>

#### *HRQoL impairment in chronic inducible urticaria*

HRQoL impairment in CIndU is determined by the required avoidance of specific eliciting triggers and the resulting interference with social and daily life activities. Subjects with CSU and comorbid CIndU have a significantly lower HRQoL when compared to subjects with CSU alone.<sup>10,65</sup> The impact of delayed pressure urticaria and cholinergic urticaria is comparable to the impact of severe atopic dermatitis and is higher than psoriasis.<sup>86</sup> However, further research is required to better characterize HRQoL impairment in the various CIndU subtypes. For physicians, it is important to consider that CIndU patients are at risk of underestimating their disease burden as they

may have few signs and symptoms because of effective avoidance behaviour, although such strategies can be very impactful on HRQoL.

#### *Angioedema further deteriorates HRQoL*

HRQoL scores are lower in CSU with angioedema.<sup>87</sup> Angioedema lasts longer than wheals (up to three days), can be disfiguring and painful, particularly when localized to the hands, feet or around the joints, and limits many daily-life and working activities. In addition, facial and oral cavity swelling episodes, which often appear to put the patient at risk of breathing difficulties, may frighten the patient, and sometimes the doctor, due to fear of a possible asphyxiation.<sup>26,88</sup> This fear may prevent patients from going to sleep, wake them at night, and motivates frequent visits to the emergency room,<sup>26</sup> where systemic corticosteroids are typically prescribed<sup>88</sup>, with little impact on the course of CSU. HRQoL improves with therapy that reduces the number of days with angioedema, particularly with omalizumab.<sup>71,89</sup> Further studies are needed, for evaluating the effect of antihistamine treatment on HRQoL.(Table 2)

#### *HRQoL impairment can be assessed by patient-reported outcome measures*

Several validated patient-reported outcome measures (PROMs) are available, and guidelines recommend their use to assess and monitor HRQoL.<sup>1</sup> In patients with predominant wheals, the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) validated in different languages and populations,<sup>72,90,91,92</sup> or the Dermatology Life Quality Index (DLQI) should be administered. In patients who predominantly or only have angioedema, the Angioedema Quality of Life Questionnaire (AE-QoL) is the PROM of choice.<sup>93,94,95</sup> (Table 3)

The Cholinergic Urticaria Quality of Life Questionnaire (CholU-QoL) is the only available and validated CIndU-specific PROM,<sup>96</sup> but additional questionnaires for cold urticaria and symptomatic dermographism are under development.

In addition to HRQoL, disease control can be captured in CSU and CIndU patients with the Urticaria Control Test (UCT)<sup>97</sup> and the Angioedema Control Test (AECT),<sup>98,99</sup> which measure the level of control over signs and symptoms as well as the impact achieved by the current treatment strategy. Accordingly, the concept of HRQoL and disease control are linked, i.e. a low level of disease control goes along with high HRQoL impairment and vice versa.<sup>97,98,99,100,101</sup>

#### **Impact on sleep, family life and partners, sexual functioning, “joie de vivre”**

Pruritus and the severity of hives, as well as the fear of angioedema attacks, are mainly responsible for sleep difficulties, such as difficulty staying asleep or waking up too early, with resulting fatigue and diminished physical and emotional well-being during the day.<sup>74</sup>

CSU also affects the families and partners of patients and significantly impairs sexual functioning. Women with CSU have reduced total Female Sexual Function Index scores compared to control subjects, and 2 out of 3 female patients exhibit sexual



dysfunction, which is linked to the presence of angioedema, disease activity and also associated with anxiety, depression, fatigue and impaired QoL.<sup>75</sup>

In patients with CSU or with CIndU with a low reactivity threshold or difficulty avoiding triggers, social life, sport and leisure activities can also be significantly impaired,<sup>12</sup> contributing to reduced “joie de vivre”.

### **CU comes with impaired performance in school and at work**

CU often has a negative impact on patients’ work productivity and/or school performance, with higher impairment in patients using sedating antihistamines.<sup>102</sup> A Spanish study reported higher rates of “bad school performance” for children suffering from urticaria/angioedema or not (4.8% vs. 1.9%), and 7.4% of children missed a mean of 7.5±18.5 school days due to urticaria in the previous year. In addition, 3.3% of parents needed to take days off work because of their child’s urticaria.<sup>103</sup>

The ASSURE study demonstrated a high impact of CU on work productivity. The mean absenteeism, presenteeism (percentage impairment while working), and overall work impairment (work productivity loss) were 6%, 25%, and 27%, respectively. More than 20% of the employed patients report at least 1 hour of work lost in the previous 7 days and, among these, 62% reported missing up to one working day. The main reasons affecting patients’ capacity to work were itching (40%) and angioedema (28%).<sup>12</sup>

The AWARE study in Europe confirmed a high frequency of work-days lost due to CSU,<sup>20,21,13</sup> similarly to moderate or severe psoriasis.<sup>7</sup> In Central/South America (C/SA) the mean absenteeism, presenteeism and the overall work impairment was significantly greater compared to Europe, which was linked with a higher disease activity in the C/SA region.<sup>19</sup>

### **The burden of CU comorbidities**

Many studies have investigated the relationship of autoimmune disease and CSU.<sup>104</sup> Comorbid thyroid autoimmunity is the most frequent, with anti-thyroid autoantibodies (to thyreoperoxidase, thyroglobulin and/or TSH receptor) found in 4-37.1% of CSU patients, often in association with autoimmune thyroid disease.<sup>105</sup> In addition, a higher prevalence of systemic lupus erythematosus (26.7 times increased risk of SLE in CSU females),<sup>106</sup> type I diabetes mellitus (1.8%), vitiligo (0.4%), coeliac disease and rheumatoid arthritis (0.6%) have also been reported.<sup>12,107</sup> There is value in screening for these diseases in the diagnostic workup of CSU patients, by including targeted questions in the history.<sup>1</sup>

CSU is not an atopic disease, although atopy is frequent in CSU (16.9%).<sup>43</sup> A higher prevalence of allergic rhinitis or asthma<sup>13,16,20,21</sup> and also atopic dermatitis in children has been reported.<sup>31</sup>

Several large studies have shown an association of CSU with hypertension and obesity (>20%)<sup>13,19,20,21</sup>, and a few also report a higher frequency of hyperlipidaemia as well as metabolic syndrome.<sup>108,109</sup>

Given the debilitating nature of CSU, it is not surprising that more than 30% of patients experience psychiatric comorbidities including anxiety, depression, and somatoform disorders with a significant negative impact on their QoL.<sup>13,20,110,111</sup>

An association between CSU and headaches has been reported, which can affect QoL, particularly in children.<sup>112</sup>

There is a discussed link between CSU and *Helicobacter pylori* infection,<sup>113</sup> parasitic infections,<sup>114</sup> chronic viral infections including hepatitis B and C virus and Human Herpes virus 6.<sup>115,116</sup>

Rarely, reports have linked CSU to papillary thyroid, lung and hematologic malignancies.<sup>117,118</sup>

### **CU comes with high costs for patients and society**

Direct costs of CSU (e.g. medication, regular outpatient visits, emergency room treatment, hospitalization, laboratory tests) are high. Recent studies estimated the mean total direct costs per patient per year to be around 900 purchasing power parity dollars (PPP\$) in Italy and PPP\$ 2.400 in France with therapies and inpatient costs being the major contributing factors.<sup>12,107</sup> Indirect costs per patient per year were found to be even higher and ranged from around PPP\$ 6.550 in France to PPP\$ 15.550 in Germany, with work productivity loss (mainly presenteeism) as the main driver.<sup>12</sup> High costs have also been estimated for Asia.<sup>119</sup> In the US, CU patients had higher rates of health care resource utilization relative to controls (incidence rate ratios of 1.71, 2.39, and 2.07 for inpatient, emergency, and outpatient visits, respectively), and higher all-cause per patient per year costs (mean cost differences of PPP\$ 2.090, PPP\$ 1.606, and PPP\$ 483 for total, medical, and pharmacy costs, respectively).<sup>120</sup>

CSU treatment costs can be high, particularly for omalizumab, but a study from the Netherlands has shown that, compared to first and second line therapy, omalizumab is cost-effective due to its high efficacy and safety and subsequent reduction of healthcare resource consumption and lower indirect costs related to absenteeism and presenteeism.<sup>121</sup> No direct comparative studies have been performed with ciclosporin, which is less expensive than omalizumab but comes with a lower percentage of complete responders (17% vs 43% in a small retrospective study looking at the two populations in parallel),<sup>122</sup> and regular blood pressure measurements and blood monitoring are necessary to detect potentially serious adverse effects.

It is very difficult to compare the economic costs of CU with other diseases, due to different health-care realities in each country and different calculation techniques used. However, the economic burden reported for CU seems similar to that of psoriasis in the US (approximately \$6.290/patient/year in 2013) and in Germany (around \$6.200±\$9.020),<sup>123</sup> and to the burden of moderate-to-severe atopic dermatitis, where direct, indirect and out-of-pocket-costs calculated for patients in Germany were around \$8.315/patient/year.<sup>124</sup>

### **Summary, conclusions, outlook and unmet needs and future challenges**

CSU and CIndU are highly prevalent and long-lasting diseases that impact all age groups worldwide. They are associated with a high burden for the patient, their family

and partners as well as for health care systems and the entire society. Moreover, as there is usually no identifiable cause that can be eliminated and, therefore, no curative treatment, continuous and high-cost medication is frequently needed to control the symptoms and improve QoL.

Better epidemiological studies on disease prevalence and incidence across all age groups from all areas of the globe with a high number of patients are needed. Also, more accurate information is necessary on disease duration, severity, comorbidities, impact on QoL, laboratory results, and response to treatment according to gender and age. We also need more information on special populations (pregnant and nursing mothers), the different subgroups of CSU that have already been identified (type IIb autoimmune or autoallergic CSU), and the different types of CIndU (dermographism, cholinergic urticaria, cold-induced urticaria, pressure urticaria, solar urticaria). This will be possible only if physicians and centres managing CU work together, like in the network of UCAREs (Urticaria Centres of Reference and Excellence)<sup>125</sup>, and contribute cases to multicentre studies and registries like CURE (Chronic Urticaria Registry).<sup>126</sup> This will allow for the collection of big data to better characterize different CU phenotypes, their pathomechanisms and, accordingly, define optimal treatment strategies that will improve the prognosis and reduce the burden of CU.

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## Figure legends

Fig 1. The burden of Chronic Urticaria from the patient's perspective and the main aspects that impact the quality of life.

The impact of chronic urticaria on individual patients' lives and society at large is substantial and must be seen as the sum of the wide spectrum of effects the disease has, including those on emotional, social, financial and physical aspects of the patient's everyday life and its impact on health care system resources. <sup>1</sup> Chronic urticaria comes with high costs, for patients and society, that are driven by medication, outpatient visits, emergency room treatments, hospitalizations, laboratory tests, and work productivity loss (mainly presenteeism). <sup>2</sup> Comorbidities include other forms of chronic urticaria, another autoimmune disease (most commonly autoimmune thyroiditis), depression, anxiety, with each of these comorbidities affecting up to third of patients with chronic urticaria. <sup>3</sup> Recurrent angioedema affects more than half of patients with chronic urticaria and further deteriorates their QoL. Recurrent angioedema can come with or without recurrent whealing, the former is more common than the latter.

Fig 2. Prevalence of chronic urticaria in the world, according to Fricke et al.<sup>4</sup>

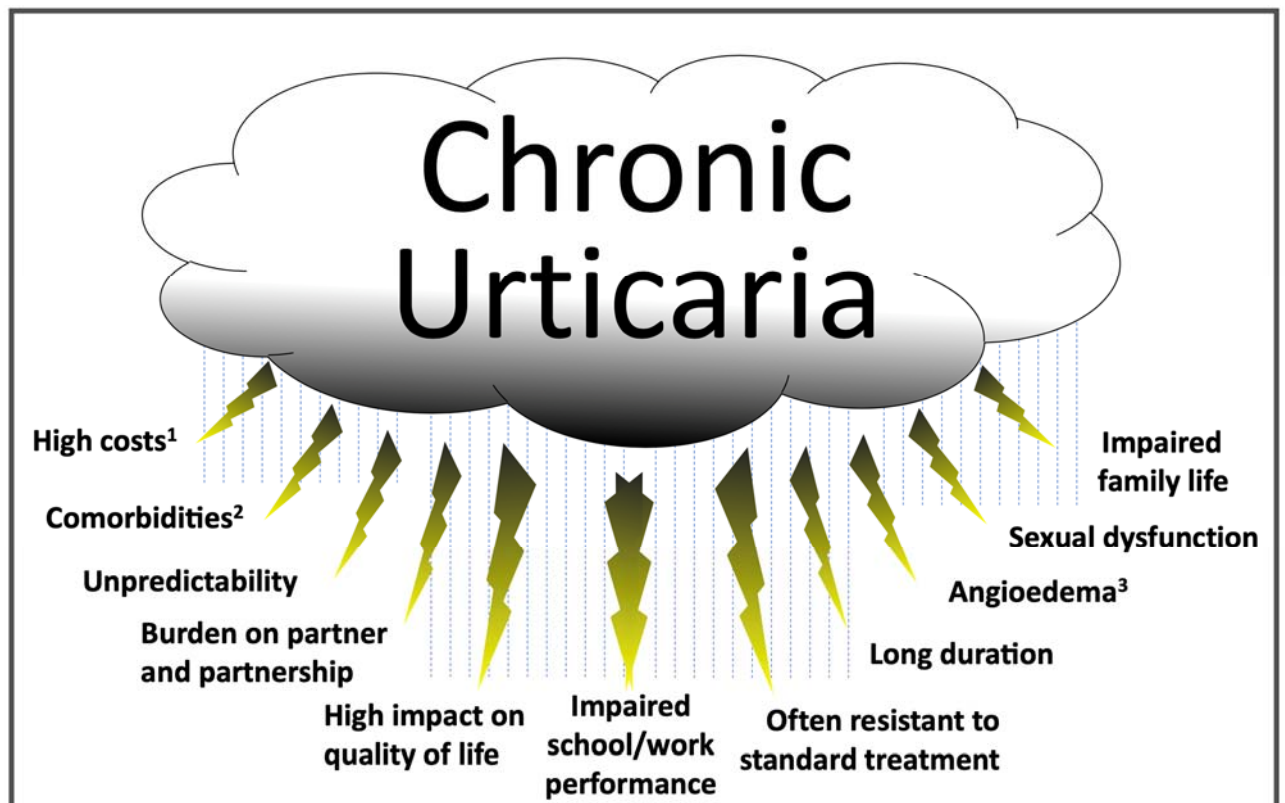


Figure 1

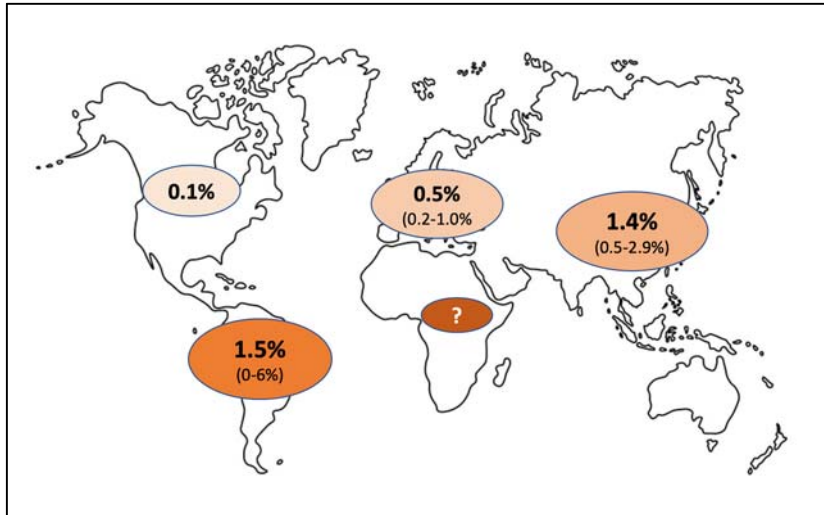


Figure 2

Table 1 – Main aspects of chronic urticaria that contribute to the disease burden for the society

<b>Aspects of CU burden</b>	<b>Quantification</b>
High disease prevalence (all ages, mainly female)	4.4% (lifetime prevalence) 0.1-1.5% (point prevalence)
Long disease duration	Mean 11.5±10.8 years in adults
Lack of curative therapy	No symptomatic response to 1 <sup>st</sup> /2 <sup>nd</sup> line therapy in > 25%
Health care resources (direct costs in Europe)	PPP\$900 - 2.400 / year / patient
Indirect cost (in Europe) Loss of work productivity (mainly presenteeism)	PPP\$6.550 - 15.550 / year / patient

PPP\$- purchasing power parity dollars



Table 2 – Main aspects of chronic urticaria that impact patient’s health-related quality of Life (HR-QoL)

<b>Aspects of CU</b>	<b>Impact on HRQoL</b>
Disease duration > 1 year in > 25% of patients > 5 years in > 10% of patients	Long disease course Affects many years of patient’s life
Delay in correct diagnosis/management often > 1-2 years	Frustration Patients stop seeking medical care
No identifiable cause/trigger in CSU	Unpredictability Affects programming daily activities/life
Itch	Distressing, disturbing Impact on sleep and daily activities
Intensity of wheals	Visibility of lesions Loss of working/school days
Daily urticarial lesions	Impact on life with family and friends Impact on sexual activity Impact on sports/leisure activities Impact on choice of clothes
Angioedema may last 24-72 hours	Fear of asphyxiation Difficulty in eating/swallowing Pain, impaired function Visibility, shame
Concomitant CIndU	Need for avoidance attitudes (cold, heat, sun, exercise, pressure, friction)
Impaired sleep	Impaired performance at school and work
Comorbidities	Auto-immune diseases (e.g.thyroid disease) Atopic diseases Anxiety and depression

Table 3 – Patient reported outcome measures validated in many languages and recommended in the guidelines to evaluate disease activity and Health-related Quality of Life (HR-QoL)<sup>1</sup>

PROM	Scores
UAS7 - Urticaria Activity Score for 7 days <sup>127</sup> Evaluates daily intensity of itch (0-3) and number/size of wheals (0-3)	Well controlled disease: 0-6 Mild disease: 7-15 Moderate disease: 16-27 Severe disease: 28-42
AAS - Angioedema Activity Score <sup>128</sup> Evaluates daily occurrence of angioedema, its duration, physical discomfort caused, impact on daily activities, impact on appearance and overall severity	AAS for 4, 8 and 12 weeks
UCT - Urticaria Control Test <sup>97</sup> Evaluates activity of wheals, angioedema and itch, impact on QoL, effect of treatment and overall disease control during the previous 4 weeks	0 – No disease control ≤ 11 bad disease control ≥12 good disease control
CU-Q2oL - Chronic Urticaria Quality of Life Questionnaire <sup>72</sup> 23 questions on 6 domains (itch, swellings, impact on life activities, sleep problems, looks and limits)	Good correlation with DLQI (Dermatology Life Quality Index)
AE-QoL – Angioedema quality of life <sup>94</sup> 17 questions for 4 domains (functioning, Fatigue/mood, Fears/shame and food)	