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REVIEW ARTICLE

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The global burden of chronic urticaria for the patient and society*

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Summary

Chronic urticaria (CU) affects about 1% of the world population of all ages, mostly young and middle-aged women. It 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_1-antihistamines, even at higher doses, and third- and fourth-line therapies (omalizumab and ciclosporin) control the disease only in two-thirds of H_1-antihistamine-resistant patients. Here we review the impact of CU on different aspects of patients' quality of life and the burden of this chronic disease for the patient and society. CU may have a strong impact on health-related quality of life (HRQoL), particularly when CSU is associated with angio-oedema and/or CIndU (Dermatology Life Quality Index > 10 in 30% of patients). Comorbidities, such as anxiety and depression, which are present in more than 30% of patients with CSU, compound HRQoL impairment. Severe pruritus and the unpredictable occurrence of weals and angio-oedema 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 patients' performance at school and

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work (6% absenteeism and 25% presenteeism). Apart from treatment costs, with annual values between 900 and 2400 purchasing power parity dollars (PPP$) in Europe and the USA, CU is associated with a high consumption of medical resources and other indirect costs, which may reach a total annual cost of PPP$ 15 550.

Chronic urticaria (CU) is defined by the occurrence of weals (hives), angio-oedema or both for more than 6 weeks. Lesions occur 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).[1] Autoimmunities of type I (autoallergy with IgE autoantibodies to interleukin-24, thyroid peroxidase, 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,[2] but other mechanisms of mast cell activation and modulation[3] and other elicitors, like nonsteroidal anti-inflammatory drugs, are also involved.[1]

CU is a common disease worldwide[4] that affects people of all ages. It has a variable duration but can last for several years.[5] CU has a significant impact on health-related quality of life (HRQoL),[6] similar to or greater than moderate-to-severe psoriasis,[7] atopic dermatitis, asthma and severe coronary artery disease requiring bypass grafting.[6,8–11] 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.[12,13] Because CU carries a significant humanistic and economic burden,[14] this review will discuss the spectrum of detrimental consequences that CU has on patients, healthcare systems and societies on a global scale (Figure 1 and Table 1).

The authors worked in groups of three to review the literature considered relevant for each of the sections, and the leading authors (M.G., A.G-A. and M.M.) composed the final document, which was further reviewed and approved by all of the authors.

The prevalence of chronic urticaria in the world is high and increasing

CU is common in every country globally, and its prevalence has increased 2–10-fold over the last decade.[4,15–17] 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 1·5% and 1·4% in Latin American and Asian countries, respectively.[4] Prevalence data from Africa are lacking, but people of all ethnicities appear to be affected, although the prevalence may vary in different populations due to either genetics or lifestyle habits (Figure 2).

CU affects mainly young-to-middle-aged adults,[13] with a mean age of onset in patients in their late twenties to forties.[18–21] 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,[22] and 1% for children under 14 years.[23] Data on elderly patients are largely lacking, but patients aged ≥ 65 years represent 10–21·7% of cases of CU.[24,25]

CU, and especially CSU, is more common in women (up to 80%),[12,18–20,25] but this sex difference is not apparent in children under 15 years[4,23] or in the elderly,[24] and it is also less evident in Asian populations.[4]

The real prevalence of CSU with isolated angio-oedema (without weals) is not known but it is considered to account for about 10% of all cases of CSU.[26,27] It is less common than presentation with angio-oedema and weals together, and weals alone. In patients with recurrent angio-oedema without weals, hereditary variants need to be ruled out, by history taking and appropriate follow-up diagnostics.[1] Such variants include hereditary angio-oedema, and other forms of bradykinin-mediated angio-oedema, such as angiotensin-converting enzyme inhibitor-induced angio-oedema.

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

Patients with chronic urticaria face long delays in diagnosis and treatment

The diagnosis of CSU is relatively easy to make. A simple set of clinical and laboratory investigations excludes urticaria mimickers, such as urticarial vasculitis and autoinflammatory syndromes in patients with urticarial weals, as well as bradykinin-mediated angio-oedema in patients with isolated swellings.[1,32] 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,[12] for Central/South America 3 years and for Western Europe 2–4 years.[19] In the USA, it takes more than 6 weeks to see a physician or consult

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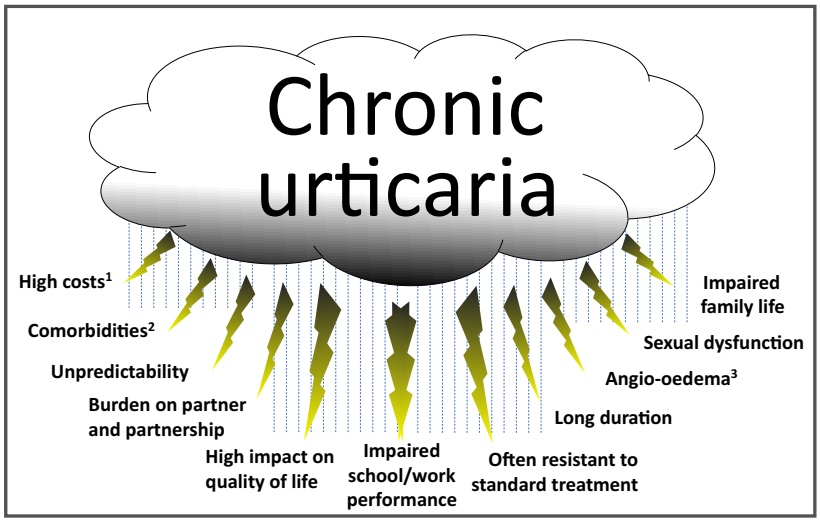

Figure 1 The burden of chronic urticaria from the patient's perspective and the main aspects that impact quality of life. The impact of chronic urticaria on individual patients' lives and society at large is substantial and must be seen as the sum of the wide spectrum of effects the disease has, including those on emotional, social, financial and physical aspects of the patient's everyday life and the impact on healthcare system resources. [1]Chronic urticaria comes with high costs, for patients and society, which are driven by medication, outpatient visits, emergency room treatments, hospitalizations, laboratory tests, and work productivity loss (mainly presenteeism). [2]Comorbidities include other forms of chronic urticaria, another autoimmune diseases (most commonly autoimmune thyroiditis), depression and anxiety, with each of these comorbidities affecting up to one-third of patients with chronic urticaria. [3]Recurrent angio-oedema affects more than half of patients with chronic urticaria and further deteriorates their quality of life. Recurrent angio-oedema can come with or without recurrent wealing; the former is more common than the latter

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

Aspects of chronic urticaria burden	Quantification
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 first- and second-line therapy in> 25% of cases
Healthcare resources (direct costs in Europe)	PPP$ 900–2400 per year per patient
Indirect cost (in Europe) Loss of work productivity (mainly presenteeism)	PPP$ 6550–15 550 per year per patient

PPP$, purchasing power parity dollars.

with a specialist in about 45% of patients with CU,[33] whereas in Japan 85% of patients consulted an allergist or dermatologist within 1 month from the onset of urticaria.[34]

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 (i.e. food allergy).[18,33,35] This leads to significant frustration in up to 67% of patients,[36] not to mention the high consumption of medical resources with no additional benefit.[37] Also, as physicians are frequently unaware of urticaria guidelines,[38] they may give misinformation concerning the risk of anaphylaxis and recommend, inappropriately, first-generation sedating antihistamines, on-demand treatment only or the prolonged use of systemic corticosteroids.[13,18,20] As a consequence, many patients get frustrated and stop seeking treatment, and surveys indicate that >50% are not under the care of a physician.[18]

Chronic urticaria 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,[18] with remission occurring within 1 year after onset only in 20–75%[27,39] and within 5 years in only 30–55%.[10,40,41]

Clinical predictors of longer duration include insufficient response to a standard-dosed antihistamine (51% and 66% persistence at 2 and 5 years, respectively),[42] late onset (> 45 years),[43] concomitant CIndU,[43] intolerance to nonsteroidal anti-inflammatory drugs,[44] and a relapsing course,[40,43] defined as CU recurring at least 6 months after symptom resolution and cessation of controller therapy.[45,46] Some laboratory biomarkers (high C-reactive protein and D-dimers) may predict disease severity[47] 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.[2]

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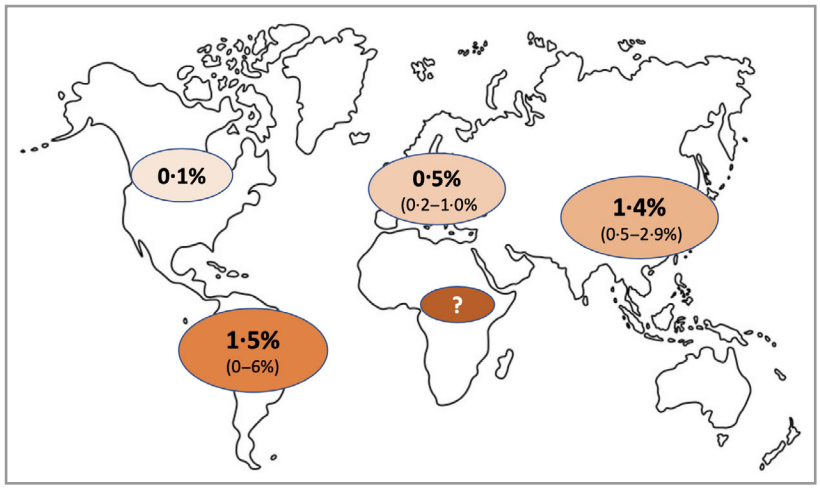

Figure 2 Prevalence of chronic urticaria across the world, according to the results of Fricke *et al.*[4] The data are the point prevalence estimate, with the 95% confidence interval in brackets

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

The resolution rate of CU in children is also low, with studies reporting a 10% resolution rate per year in Canada[31] and remission rates in Asia of 19%, 54% and 68% at 1, 3 and 5 years, respectively.[50] Data on disease duration in elderly patients 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,[41,45,51] and many calculations on disease duration consider the first consultation as the disease start, which is not reflective of the true CU onset.

Chronic urticaria is often resistant to standard treatment

On average, only 50% of patients with CSU have an adequate response to nonsedating antihistamines at standard or up to fourfold doses,[52–54] and this percentage is even lower when angio-oedema is also present.[55] However, response rates do vary greatly across studies. A recent observational study demonstrated very low rates of disease control with standard-dosed nonsedating antihistamines (18%), but favourable outcomes with higher doses in 74% of patients.[55] In a systematic review, 60% of patients were unresponsive to standard-dosed nonsedating antihistamines, and updosing controlled pruritus but not the number of weals.[5]

Up to one in four patients require treatment with omalizumab or ciclosporin, the third- and fourth-line therapies, respectively, according to the EAACI/GA^{2}LEN/EDF/WAO urticaria guideline.[1] 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.[56–58] In contrast, patients with type IIb autoimmune CSU, who have a positive ASST and BAT/BHRA, more often exhibit basopenia and eosinopenia, often with a low or very low serum IgE, and show a slow and poorer response to omalizumb[2,56] but a good treatment outcome with ciclosporin.[59,60]

Although there are fewer studies in children, resistance to H_1-antihistamines also occurs, even after updosing,[61,62] and management should follow the recommendations for adults, adjusted for age and weight.[1]

The impact of angio-oedema

There is some variation in the numbers of patients with CSU experiencing both hives and angio-oedema or angio-oedema alone. Angio-oedema is reported in approximately 40–60% of patients with CU,[19–21,63] but angio-oedema may be underdiagnosed, with patients reporting it more often than their physicians (65·8% vs. 41%).[26,64] The average intensity of angio-oedema during the previous 6 months was rated as severe, moderate, mild and negligible by 31%, 46%, 20% and 2% of patients, respectively.[64]

Compared with CSU with weals alone, the occurrence of angio-oedema is associated with a prolonged disease duration (persistent symptoms at 1 year in 43–48% vs. 64–70%),[27] more severe disease,[26] poorer response to antihistamines[65,66] and worse HRQoL.[26]

Chronic urticaria comes with high quality-of-life impairment

Health-related quality-of-life impairment in chronic spontaneous urticaria

HRQoL is substantially affected in patients with CSU.[27] Compared with other skin disorders, CSU is among those with the

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Table 2 Main aspects of chronic urticaria that impact patients' health-related quality of life (HRQoL)

Aspect of chronic urticaria	Impact on HRQoL
Disease duration > 1 year in > 25% of patients > 5 years in > 10% of patients	Long disease course. Affects many years of a patient's life
Delay in correct diagnosis and management Often > 1–2 years	Frustration. Patients stop seeking medical care
No identifiable cause or trigger in chronic spontaneous urticaria	Unpredictability. Affects programming daily activities and life
Itch	Distressing, disturbing. Impact on sleep and daily activities
Intensity of weals	Visibility of lesions. Loss of working or school days
Daily urticarial lesions	Impact on life with family and friends. Impact on sexual activity. Impact on sports and leisure activities. Impact on choice of clothes
Angio-oedema May last 24–72 h	Fear of asphyxiation. Difficulty in eating or swallowing. Pain, impaired function. Visibility, shame
Concomitant chronic inducible urticaria	Need for avoidance attitudes (cold, heat, sun, exercise, pressure, friction)
Impaired sleep	Impaired performance at school and work
Comorbidities	Autoimmune diseases (e.g. thyroid disease). Atopic diseases. Anxiety and depression

highest HRQoL impairment,[6–8] with Dermatology Life Quality Index >10 in >30% of patients referred to urticaria clinics.[13,19,20] The main factors responsible for the physical, social and emotional impact of CSU include the sudden and unpredictable appearance of weals and angioedema,[67] and itch, which is very distressing and has a major impact on sleep and patients' wellbeing.[68,69] Many patients with CSU have daily or almost-daily signs and symptoms,[67] which often occur during the evening, night time or early morning,[70] but their exact timing and location, duration and severity can change considerably from day to day.[67] Accordingly, patients affected by CSU live in a constant expectation of newly appearing weals and angio-oedema,[10] including the fear of suffocation,[71] and many patients have a feeling of losing control over their lives.[10] Further negative emotions include self-consciousness and embarrassment,[10] frustration,[10] feeling sad and discouraged,[7,72] and being tired and irritable,[10] weak[10] and anxious.[7,10,12,33] This is often further exacerbated by underestimation of the disease burden by others, including treating physicians.[26,33] CSU leads to an impairment of sleep and cognitive functions,[7,10,12,70,73] and has a major impact on social interactions,[9] work performance[7,12] and daily-life functioning,[10,12] including interpersonal relationships and sex life.[10,74]

HRQoL impairment correlates generally with disease activity;[12,75,76] however, there must be additional influencing factors as correlation with the Urticaria Activity Score for 7 days is not high.[75–77] Age and sex have an impact on some dimensions of HRQoL,[78,79] but a major driver is psychiatric comorbidities, such as anxiety and depression, which induce stronger HRQoL impairment.[80–84]

Health-related quality-of-life 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. People with CSU and comorbid CIndU have a significantly lower HRQoL than those with CSU alone.[10,65] The impact of delayed-pressure urticaria and cholinergic urticaria is comparable with the impact of severe atopic dermatitis and is higher than that of psoriasis.[85] However, further research is required to characterize better the HRQoL impairment in the various CIndU subtypes. For physicians, it is important to consider that patients with CIndU 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.

Angio-oedema further deteriorates health-related quality of life

HRQoL scores are lower in CSU with angio-oedema.[86] Angio-oedema lasts longer than weals (up to 3 days), can be disfiguring and painful – particularly when localized to the hands and 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 possible asphyxiation.[26,87] This fear may prevent patients from going to sleep or wake them at night, and motivates frequent visits to the emergency room[26] where systemic corticosteroids are typically prescribed,[87] with little impact on the course of CSU. HRQoL improves with therapy that reduces the number of days with angio-oedema, particularly with omalizumab.[71,88] Further studies are needed to evaluate the effect of antihistamine treatment on HRQoL (Table 2).

Health-related quality-of-life 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

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and monitor HRQoL.[1] In patients with predominant weals, the Chronic Urticaria Quality of Life Questionnaire, validated in different languages and populations,[72,89–91] or the Dermatology Life Quality Index should be administered. In patients who predominantly or only have angio-oedema, the Angioedema Quality of Life Questionnaire is the PROM of choice (Table 3).[92–94]

The Cholinergic Urticaria Quality of Life Questionnaire is the only available and validated CIndU-specific PROM,[95] but additional questionnaires for cold urticaria and symptomatic dermographism are under development.

In addition to HRQoL, disease control can be captured in patients with CSU and CIndU with the Urticaria Control Test[96] and the Angioedema Control Test,[97,98] which measure the level of control over signs and symptoms, as well as the impact achieved by the current treatment strategy. Accordingly, the concepts of HRQoL and disease control are linked, where a low level of disease control goes along with high HRQoL impairment and vice versa.[96–100]

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

Pruritus and the severity of hives, as well as the fear of angio-oedema 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.[73]

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 with controls, and two out of three female patients exhibit sexual dysfunction, which is linked to the presence of angio-oedema and disease activity, and is also associated with anxiety, depression, fatigue and impaired QoL.[74]

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,[12] contributing to reduced *joie de vivre*.

Chronic urticaria 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.[101] A Spanish study reported higher rates of 'bad school performance' for children with CU (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.[102]

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 employed patients report at least 1 h 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 angio-oedema (28%).[12]

The AWARE study in Europe confirmed a high frequency of workdays lost due to CSU,[13,20,21] similarly to moderate or severe psoriasis.[7] In Central/South America the mean absenteeism, presenteeism and overall work impairment were significantly greater than in Europe, which was linked with higher disease activity in the Central/South American region.[19]

The burden of chronic urticaria comorbidities

Many studies have investigated the relationship of autoimmune disease and CSU.[103] Comorbid thyroid autoimmunity is the most frequent, with antithyroid autoantibodies (to thyroid peroxidase, thyroglobulin and/or thyroid-stimulating receptor receptor) found in 4–37·1% of patients with CSU, often in

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[1]

Patient-reported outcome measure	Scores
UAS7: Urticaria Activity Score for 7 days.[127]	Well controlled disease: 0–6
Evaluates daily intensity of itch (0–3) and number and size of weals (0–3)	Mild disease: 7–15
	Moderate disease: 16–27
	Severe disease: 28–42
AAS: Angioedema Activity Score[128]	AAS for 4, 8 and 12 weeks
Evaluates daily occurrence of angio-oedema, its duration, physical discomfort caused, impact on daily activities, impact on appearance and overall severity	
UCT: Urticaria Control Test[96]	0: no disease control
Evaluates activity of weals, angio-oedema and itch, impact on quality of life, effect of treatment and overall disease control during the previous 4 weeks	≤ 11: bad disease control
	≥ 12: good disease control
CU-Q_2oL: Chronic Urticaria Quality of Life Questionnaire[72,89–91]	Good correlation with Dermatology Life Quality Index
23 questions in six domains (itch, swellings, impact on life activities, sleep problems, looks and limits)	
AE-QoL: Angioedema Quality of Life[94]	
17 questions in four domains (functioning, fatigue/mood, fears/shame and food)	

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association with autoimmune thyroid disease.[104] In addition, higher prevalences of systemic lupus erythematosus (26·7 times increased risk in female patients with CSU),[105] type I diabetes mellitus (1·8%), vitiligo (0·4%), coeliac disease and rheumatoid arthritis (0·6%) have also been reported.[12,106] There is value in screening for these diseases in the diagnostic investigation of patients with CSU, by including targeted questions in the history.[1]

CSU is not an atopic disease, although atopy is frequent in CSU (16·9%).[43] A higher prevalence of allergic rhinitis or asthma[13,16,20,21] and also atopic dermatitis in children has been reported.[31]

Several large studies have shown an association of CSU with hypertension and obesity (> 20%),[13,19–21] and a few also report a higher frequency of both hyperlipidaemia and metabolic syndrome.[107,108]

Given the debilitating nature of CSU, it is not surprising that >30% of patients experience psychiatric comorbidities including anxiety, depression and somatoform disorders, with a significant negative impact on their QoL.[13,20,109,110]

An association between CSU and headaches has been reported, which can affect QoL, particularly in children.[111] There is a discussed link between CSU and *Helicobacter pylori* infection,[112] parasitic infections[113] and chronic viral infections including hepatitis B and C virus and human herpesvirus 6[114,115] Rarely, reports have linked CSU to papillary thyroid, lung and haematological malignancies.[116,117]

Chronic urticaria 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$) in Italy and PPP$ 2400 in France, with therapies and inpatient costs being the major contributing factors.[12,106] Indirect costs per patient per year were found to be even higher and ranged from around PPP$ 6550 in France to PPP$ 15 550 in Germany, with work productivity loss (mainly presenteeism) as the main driver.[12] High costs have also been estimated for Asia.[118] In the USA, patients with CU had higher rates of healthcare 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$ 2090, PPP$ 1606 and PPP$ 483 for total, medical and pharmacy costs, respectively).[119]

CSU treatment costs can be high, particularly for omalizumab, but a study from the Netherlands has shown that, compared with first- and second-line therapy, omalizumab is cost-effective due to its high efficacy and safety, subsequent reduction of healthcare resource consumption and lower indirect costs related to absenteeism and presenteeism.[120] 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),[121] 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 those of other diseases, due to different healthcare realities in each country and different calculation techniques used. However, the economic burden reported for CU seems similar to that of psoriasis in the USA (approximately USD6290 per patient per year in 2013)[122] and in Germany (around USD6200 ± 9020),[123] 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 USD8315 per patient per year.[124]

Summary, conclusions, outlook, unmet needs and future challenges

CSU and CIndU are highly prevalent and long-lasting diseases that impact people of all age groups worldwide. They are associated with a high burden for patients, their families and their partners, as well as for healthcare 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 people of 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 sex 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, as they do in the network of UCAREs (Urticaria Centers of Reference and Excellence),[125] and contribute cases to multicentre studies and registries like CURE (Chronic Urticaria Registry).[126] This will allow for the collection of big data to characterize better the different CU phenotypes and their pathomechanisms and, accordingly, to define optimal treatment strategies that will improve the prognosis and reduce the burden of CU.

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Appendix 1: Conflicts of interest

M.G. has been a consultant and/or speaker for Novartis, Sanofi and Roche. A.G-A. has been a medical advisor for Uriach Pharma, Genentech, Novartis, FAES, GSK and Sanofi; received research grants from Uriach Pharma, Novartis and Instituto Carlos III-FEDER; and been involved in educational activities for Uriach Pharma, Novartis, Genentech, Menarini, LEO Pharma, GSK, MSD, Almirall and Sanofi. M.A-A. has received honoraria for lectures from Novartis and Sanofi. M.B-S. has received honoraria for lectures and advisory boards from Novartis. J.A.B. has been a consultant, speaker and principal investigator for Novartis, Genentech, Sanofi-Regeneron and AstraZeneca; and a consultant and principal investigator for Allakos. L.F.E. has been a consultant, speaker and principal investigator for Novartis, Sanofi and Takeda. D.F. has received honoraria for lectures and advisory boards from Novartis, Sanofi Shire (Takeda) and CSL Behring. C.A.G. has received honoraria for lectures from Novartis and Sanofi. C.G. has been a speaker for Novartis and a consultant for Celltrion, Blueprint Medicines and Argenx. M.H. has received honoraria for lectures from Kaken Pharmaceutical, Kyorin Pharmaceutical, Kyowa Hakko Kirin, Maruho, MDS, Mitsubishi Tanabe Pharma, Sanofi K.K., Torii Pharmaceutical, Taiho Pharma, Teikoku Seiyaku and Uriach. C.H.K. has received institutional funding from Novartis, Sanofi, Takeda and CSL Behring for clinical trials; and honoraria for advisory board participation and lectures and institutional funding for trials from Biocryst. E.K. has received honoraria for lectures and advisory boards from Novartis, Sanofi and Bayer. K.K. has received honoraria for educational lectures from Menarini and Novartis. I.N. has received honoraria for lectures from Novartis and been a medical advisor for Novartis and Sanofi. J.P. has received institutional funding from Novartis and Sanofi for clinical trials; honoraria for lectures from Sanofi, Novartis, Jansen and CSL Behring; and institutional funding for trials from Biocryst. P.S. has received research funding and/or fees for consulting/or lectures from Genentech, Novartis, MSD, UCB, Karrer, LEO, Shire, AbbVie, Sobi, CSL Behring, Leti, Pfizer, Janssen, Astellas, Celgene and Lilly. K.W. is or recently was a speaker and/or advisor for and/or has received research funding from Dr. R. Pfleger, Esses Pharma (now MSD), Novartis, UCB, Uriach and MOXIE. M.M. is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Amgen, Aralez, ArgenX, AstraZeneca, Celldex, Centogene, CSL Behring, FAES, Genentech, GI Innovation, Innate Pharma, Kyowa Kirin, LEO Pharma, Lilly, Menarini, MOXIE, Novartis, Roche, Sanofi/Regeneron, Third Harmonic Bio, UCB and Uriach. K.G., M.K., I.M. and L.W. declare they have no conflicts of interest.

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