

REVIEW ARTICLE

Unmet clinical needs in chronic spontaneous urticaria. A GA²LEN task force report¹

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Abstract

Chronic spontaneous urticaria, formerly also known as chronic idiopathic urticaria and chronic urticaria (CU), is more common than previously thought. At any time, 0.5–1% of the population suffers from the disease (point prevalence). Although all age groups can be affected, the peak incidence is seen between 20 and 40 years of age. The duration of the disease is generally 1–5 years but is likely to be longer in more severe cases, cases with concurrent angioedema, in combination with physical urticaria or with a positive autologous serum skin test (autoreactivity). Chronic spontaneous urticaria has major detrimental effects on quality of life, with sleep deprivation and psychiatric comorbidity being frequent. It also has a large impact on society in terms of direct and indirect health care costs as well as reduced performance at work and in private life. In the majority of patients, an underlying cause cannot be identified making a causal and/or curative treatment difficult. **Nonsedating H₁-antihistamines are the mainstay of symptomatic therapy, but treatment with licensed doses relieves symptoms effectively in < 50% of patients. Although guideline-recommended up dosing up to fourfold increases symptom control in many patients, a substantial number of patients have only little benefit from H₁-antihistamines. Consequently, there is a great need for new therapeutic strategies.**

Urticaria is one of the most frequent skin diseases. It is characterized by pruritic wheal and flare-type skin reactions with or without angioedema that usually persist for <24 h. In some patients, only angioedema is present. According to the current EAACI/GA2LEN/EDF/WAO guideline, urticaria can be classified into spontaneous urticaria, physical urticaria and other urticaria types (1). Spontaneous urticaria is further divided into acute and chronic spontaneous urticaria (disease duration for less and more than 6 weeks, respectively). The physical and other urticaria types share the attribute that symptoms are induced by different triggers, e.g. low temperatures, heat, pressure or exercise (2). In contrast, in spontaneous urticaria the lesions usually occur without an obvious stimulus. In the last consensus meeting for the current guidelines, the term 'spontaneous' was added to the previous term 'chronic urticaria', formerly also known as chronic idiopathic urticaria, CIU or CU, to emphasize that wheals develop spontaneously, i.e. independent of external stimuli.

Chronic spontaneous urticaria is by far the most common subtype of all forms of nonacute urticaria. It is characterized by the spontaneous occurrence of symptoms for more than 6 weeks. Usually, it is not easy to care for these patients. The frequent failure to identify a specific underlying cause, the unpredictable course of symptoms and a high disease burden lead to a frustration of patients and their treating physicians. The lack of efficacy of approved standard therapies in many patients is another major problem. After the development of the current guidelines, in this report we will focus on the current knowledge of prevalence, disease duration, impact of the disease on patients and society as well as the efficacy of the current standard therapies in chronic spontaneous urticaria. Finally, we will address the unmet clinical needs of patients with chronic spontaneous urticaria.

Prevalence of chronic spontaneous urticaria

Urticaria is widely held to be one of the most frequent diseases leading to a consultation of general practitioners, paediatricians, dermatologists, allergists and medical emergency facilities. Consequently, it is surprising that only a few good studies investigating the prevalence of urticaria have been published. Furthermore, most data relate to highly selected patient populations with only a few authors attempting to assess prevalence in the total population. The previous inconsistencies in the classification of urticaria during the past decades make it additionally difficult to evaluate and compare individual studies.

How common is chronic spontaneous urticaria?

The first data on the prevalence of urticaria were published over 60 years ago. American authors found that around every fifth person will experience at least one episode of any type of urticaria during their lifetime (3, 4). A recent study from Spain found similar numbers (5). However, there are also European studies that point towards a lower lifetime prevalence (prevalence during the whole lifetime until the investigation) of around 8–10% (6–8). For nonacute urti-

caria, less information is available. Four decades ago, Hellgren found a point prevalence (prevalence at the time of the investigation) of around 0.1% in the total population of Sweden (9), while more recently Gaig and co-workers reported a point prevalence of 0.6% in the Spanish population (5). The reason for the large variations between these figures is unclear. Possible explanations include differences in the methods employed as well as geographical and cultural characteristics. An increasing incidence of urticaria diseases during the past decades might also be discussed.

Chronic spontaneous urticaria as well as physical urticaria and other (inducible) urticaria that persist for more than 6 weeks can be grouped together as nonacute urticaria. At least to our knowledge, only one study examining the prevalence of chronic spontaneous urticaria with regard to the recommended classification has been published yet. This found a period prevalence of 0.8% in 1 year in Germany (8). Apart from this work, we do not have any direct information on the prevalence of chronic spontaneous urticaria in the general population. However, statistical analysis of patients presenting with nonacute urticaria suggests 66–93% have chronic spontaneous urticaria, 4–33% a physical urticaria and 1–7% cholinergic urticaria (10–15). A limitation of many studies is that they give no information about how they evaluate combinations, e.g. of chronic spontaneous urticaria and physical urticaria. In fact, a combination of chronic spontaneous urticaria and other urticaria types is not uncommon. A selection of important studies on the prevalence and distribution of urticaria is presented in Table 1.

Clinically, chronic spontaneous urticaria patients can be further divided into those with concomitant angioedema, those without angioedema and those with recurrent angioedema without wheals. In summary, the available data suggest that 33–67% of all patients with chronic spontaneous urticaria exhibit wheals and angioedema, whereas 29–65% exhibit only wheals and 1–13% only angioedema. A selection of important publications can be found in Table 2 (8, 11, 12, 14, 16–19).

Urticaria is more common than previously thought and may be increasing. Up to one in four in the total population suffers from urticaria once in their lifetime. At any single time, 0.5–1.0% of the population is suffering from chronic spontaneous urticaria

Who is affected by chronic spontaneous urticaria?

The majority of studies show clearly that women suffer from urticaria nearly twice as often as men do (5, 6, 8–13, 16, 17, 20–24). This is not only true for chronic spontaneous urticaria, but also for urticaria in general. Neither the criteria for selection, nor the observed country or time of the study, seems to alter these figures.

The peak age of chronic spontaneous urticaria patients is between 20 and 40 years in most studies (11, 12, 14, 16, 19, 20, 24). This means that patients are primarily affected during important years of their working age.

Table 1 (A) Prevalence and gender ratio of urticaria in the total population; (B) Distribution of different types of urticaria in selected patients

Study	Urticaria*						Nonacute urticaria†			
	Country	Number of subjects	Lifetime prevalence (%)‡	Point prevalence (%)§	Sex ratio (f : m in %)	Mean age (in years)	Lifetime prevalence (%)‡	Point prevalence (%)§	Sex ratio (f : m in %)	Mean age (in years)
(A)										
Swinny (1941)¶	USA	1000	22.3	NR	NR	NR	NR	NR	NR	NR
Sheldon et al. (1954)**	USA	1424	15.7	NR	NR	NR	NR	NR	NR	NR
Hellgren (1972)	Sweden	36475	NR	0.1	56 : 44	44 (m), 35 (f)††	NR	0.1	NR	NR
Bakke et al. (1990)	Norway	4992	9.0	NR	61 : 39	††	NR	NR	NR	NR
Hermann-Kunz (1999)	Germany	7099	7.8	NR	69 : 31	30–35§§	NR	NR	NR	NR
Gaig et al. (2004)	Spain	5003	21.8	NR	63 : 37	††	2.9	0.6	80 : 20	NR
Zuberbier et al. (2010)	Germany	4093	8.8	NR	NR	39	1.8	0.8¶¶	70 : 30	43
(B)										
Study	Country	Number of patients		Chronic spontaneous urticaria (%)		Physical urticaria (%)***		Cholinergic urticaria (%)***		
Small et al. (1982)	Canada	231		93		6		1		
Sibbald et al. (1991)	Canada	251		69		27		4		
Barlow et al. (1993)	UK	135		93		4		3		
Humphreys and Hunter (1998)	UK	229		74		24		2		
Schnyder et al. (1999)	Switzerland	115		87		13		NR		
Kozel et al. (2001)	Netherlands	220		66		33		1		
Van der Valk et al. (2002)	Netherlands	372		NR		NR		7		
Giménez-Arnau et al. (2004)	Spain	235		71		27		3		
Kulthanan et al. (2007)	Thailand	450		90		9		1		
Ferrer (2009)	Spain	539		84		14		2		

NR, not reported.

*Comprises all types of urticaria.

†Authors do not clearly distinguish between chronic spontaneous urticaria and other forms of nonacute urticaria, except the work of Zuberbier et al.

‡Lifetime prevalence is defined as prevalence during the whole lifetime until the investigation.

§Point prevalence is defined as prevalence at the time of the investigation.

¶Swinny examined college students.

**Sheldon et al. examined non-patients.

††Authors report median instead of mean and distinguish between male and female patients.

‡‡Authors report prevalence for different age spans but give no information on mean age.

§§Authors report mean age of urticaria onset separated by different regions and by gender.

¶¶Authors report a period prevalence for active chronic spontaneous urticaria within the past 12 months.

***Percentages for physical urticaria and cholinergic urticaria represent percentages of patients with physical urticaria or cholinergic urticaria without additional chronic spontaneous urticaria. Patients with combinations of chronic spontaneous urticaria and physical urticaria or cholinergic urticaria were counted as chronic spontaneous urticaria patients.

Table 2 Frequency of angioedema in selected patients with chronic spontaneous urticaria

Study	Country	<i>n</i>	Wheals and angioedema (%)	Only wheals (%)	Only angioedema (%)
Champion et al. (1969)*	UK	554	49	40	11
Juhlin (1981)	Sweden	330	67	29	4
Quaranta et al. (1989)	USA	86	53	36	11
Sibbald et al. (1991)†	Canada	254	45	51	4
Kozel et al. (2001)†	Netherlands	220	54	33	13
Toubi et al. (2004)	Israel	139	40	NR	NR
Kulthanan et al. (2007)†	Thailand	450	34	65	1
Zuberbier et al. (2010)‡	Germany	4093	33	61	6

n, number of patients/subjects; NR, not reported.

*Authors examined patients with all types of urticaria.

†Authors do not distinguish between chronic spontaneous urticaria and other forms of nonacute urticaria.

‡Authors examined the total population.

Many diseases show a prevalence pattern that is dependent on socioeconomic status, education, ethnic background or place of residence. For urticaria, only few data are available on this issue. A German study showed that people with a high socioeconomic status and those who live in larger cities are more likely to suffer from urticaria (7). However, the deviations were not very big, and it remains unclear whether the results reflect true variations in prevalence or just differences in disease awareness. Other studies failed to show a difference in urticaria prevalence with regard to education, occupation, income, place of residence and ethnic background (5, 6, 8, 25).

All age groups can develop a chronic spontaneous urticaria. However, an incidence peak is seen between 20 and 40 years, i.e. the working population is primarily affected

Duration of chronic spontaneous urticaria

Every physician dealing with urticaria patients is familiar with the fact that the natural course of different subtypes of

urticaria varies remarkably. Although the discrimination between acute and chronic spontaneous urticaria is important for what diagnostic and therapeutic approach might be chosen, it is also strongly artificial. No one really knows which patient with acute urticaria will become chronic and how often this happens. Furthermore, little is known about the proportion of patients who will experience a relapse of their disease after remission. One of the few studies investigating the duration of urticaria in the total population was published by Gaig and co-workers. They demonstrated that 50% of patients with nonacute urticaria were symptom free after a period of 3 months and 80% after 12 months. However, they were also able to show that 11% still suffered after 5 years (5). Beyond that, various other authors have examined this issue in selected patient populations. The results vary greatly. One major reason is probably differences in patient selection. However, in summary, the data clearly show that many patients suffer for more than 1 year, while a considerable proportion suffers for much longer (10–13, 17, 18, 26). In single patients, an overall disease duration of up to 50 years was documented (26). Table 3 shows a selection of published studies.

Table 3 Duration of chronic spontaneous urticaria in selected patients

Study	Country	<i>n</i>	Cleared after 1 year (%)	Long-term course
Juhlin (1981)	Sweden	330	20	15% suffer more than 8 years
Humphreys and Hunter (1998)†	UK	365	NR	4% suffer more than 15 years
Kozel et al. (2001)	Netherlands	220	47	NR
Van der Valk et al. (2002)	Netherlands	372	NR	51% suffer more than 10 years
Toubi et al. (2004)	Israel	139	25	14% suffer more than 5 years
Gaig et al. (2004)*†	Spain	5003	80	11% suffer more than 5 years
Kulthanan et al. (2007)	Thailand	337	35	NR

n, number of patients/subjects; NR, not reported.

*Authors examined the total population

†Authors do not distinguish between chronic spontaneous urticaria and other forms of nonacute urticaria.

Studies, albeit from specialized centres, indicate that most patients suffer from chronic spontaneous urticaria for more than one year. A considerable number of patients even seem to be affected for longer than 5 years

Prognostic factors of chronic spontaneous urticaria

Because chronic spontaneous urticaria is a disease of long duration, it would be helpful to know prognostic factors that make it possible to predict the course of disease. Although the results of existing studies are inconsistent, there are four factors that seem to be associated with a long duration of urticaria: (i) disease severity, (ii) angioedema, (iii) combination of chronic spontaneous urticaria with physical urticaria and (iv) autoreactivity (positivity in the autologous serum skin test (ASST)). Some physicians believe symptomatic therapy of patients may shorten the course of the disease. However, we are not aware of any published evidence to support this.

Disease severity

The few studies that have correlated disease severity with the natural course of chronic spontaneous urticaria agree that mild symptoms go along with a shorter duration of disease (10, 18). While all patients with mild disease were symptom free after 2 years, almost 60% of those with moderate to severe disease still had symptoms (18). In addition, more than 30% of patients with moderate to severe symptoms also seemed to still suffer after 5 years (18).

Angioedema

Angioedema in chronic spontaneous urticaria patients can occur as an isolated symptom or in combination with recurrent wheals. In addition, many patients with chronic spontaneous urticaria suffer from wheals without angioedema. Interestingly, the prognosis seems to be different in these three groups. More patients with wheals and angioedema still suffer after 1 year when compared to patients who exhibit only wheals (64–70% *vs* 43–48%) (18, 19). In addition, the prognosis for the duration of symptoms seems to be even worse in patients who only develop angioedema (10, 11). For example, Kozel et al. (11) demonstrated that 80% of patients with angioedema without recurrent wheals were still affected after 12 months. In general, most studies found that around 30–50% of chronic spontaneous urticaria patients suffer from angioedema with or without wheals (8, 11, 12, 14, 18). Lower figures (20%) in Japan might point towards cultural and/or ethnic differences (27). Although the current guidelines (1) state that chronic spontaneous urticaria in some patients is characterized by angioedema without wheals, some observations indicate that angioedema alone may be another disease. Future studies will have to address this question.

Autoreactivity

It has been demonstrated that around one-third of patients with chronic spontaneous urticaria shows a positive response against their own serum in the ASST (12, 18, 22–24, 28) and that in some of these patients, it is possible to identify autoantibodies against the high-affinity IgE-receptor (FcεR1) or IgE. These functional autoantibodies can be detected by the basophil histamine release assay. While a positive ASST has only moderate specificity as a marker for these functional autoantibodies, a negative ASST has a high negative predictive value (29). In general, a positive ASST provides evidence for a circulating factor or factors that may be relevant to the understanding of the pathogenesis and management of the disease (29). All patients with a positive ASST can be subsumed to suffer from autoreactivity or autoreactive chronic spontaneous urticaria. Interestingly, most studies investigating the disease severity found that ASST-positive patients were more severely affected than ASST-negative subjects (12, 21, 23, 28), while some (12, 30), but not others (22) have associated ASST-positivity with a longer duration of disease. In addition, Staubach et al. found that ASST-positive patients require significantly more antihistaminic medication when compared to ASST-negative patients when instructed to only use short-acting antihistamines in cases of severe bouts of wheal and flare-type skin reactions (30).

Combination with physical urticaria

Reports of the prevalence of chronic spontaneous urticaria occurring in combination with physical urticaria, most commonly symptomatic dermatographism/dermatographic urticaria and delayed pressure urticaria, vary from 10% to 50% (11–14, 27). Interestingly, the overall disease duration of physical urticaria has been found to be longer than that of chronic spontaneous urticaria (10, 11). For example, cold contact urticaria and physical urticaria in general have been found to clear by 1 year in <20% (10, 11). There are also data pointing towards a longer disease duration of a combination of chronic spontaneous urticaria and physical urticaria in comparison with chronic spontaneous urticaria alone (11).

The overall duration of chronic spontaneous urticaria is likely to be longer in patients with high disease severity, angioedema, positivity of the autologous serum skin test (autoreactivity) or combination with physical urticaria

The role of stress in chronic spontaneous urticaria

While the understanding of the neuroendocrinoimmunological connections progresses, the role of stress in urticaria has regained more interest. Clearly, there is a bidirectional crosstalk between both the nervous system and the skin with, for example, nerve growth factor (a neurotrophin released during stress) being a priming agent for mast cell

activation in the skin (31). However, the relationship between stress and chronic spontaneous urticaria is not clear at the clinical level. In particular, three questions have not been answered satisfactorily: first, can stress or stressful life events lead to an outbreak of chronic spontaneous urticaria, second, can stress maintain, aggravate and/or exacerbate the symptoms of the disease, and third, does urticaria itself induce stress and if yes to what extent? One main problem here is that there is no generally accepted concept or definition of stress. In addition, it is methodologically difficult to examine the role of stress in the elicitation of urticaria, because all attempts have to be retrospective and are characterized by a considerable recall bias (32). However, some authors have tried to study the existence of stressful life events before the onset of chronic spontaneous urticaria. In a recent publication, Chung et al. found that patients with chronic spontaneous urticaria are 1.89 times more likely to have a current diagnosis of posttraumatic stress disorder in comparison with a control group. Interestingly, there was no significant association between posttraumatic stress disorder diagnosis and the severity of the disease (33). In addition, chronic spontaneous urticaria patients were found to have higher levels of life event stress and perceived stress (34). Data from other authors also show that patients with urticaria frequently have experienced stressful life events before the onset of the disease (35–37). Stress as an aggravation factor of urticaria is suspected by many patients. However, evidence from well-controlled studies is lacking. The same is true for the efficacy of a suitable psychological or psychosomatic therapy including relaxation techniques in the treatment of chronic spontaneous urticaria with only limited data pointing towards a possible beneficial effect (38, 39). Finally, there is a need for future studies that examine the role of urticaria itself as a causal factor of stress.

In summary, stress might act as a precipitating as well as an exacerbation factor in some patients suffering from chronic spontaneous urticaria. Conversely, urticaria itself is probably a major cause of stress. As yet, most of the available data are only based on anecdotal reports, uncontrolled studies or examinations with low patient numbers. Therefore, the evidence is too preliminary to provide definitive conclusions. There is an unmet need for well-controlled studies on the role of stress and its treatment in chronic spontaneous urticaria.

Stress might act as an eliciting and/or exacerbating factor in chronic spontaneous urticaria. Conversely, urticaria itself is probably a major cause of stress

Impact of chronic spontaneous urticaria

Impact on the patients

Quality of life

In addition to the classical clinical symptoms like pruritus, whealing and the occurrence of angioedema, many other fac-

tors are of major importance for patients with chronic spontaneous urticaria. These include the unpredictability of the attacks, lack of quality sleep, fatigue caused by treatment side-effects and cosmetic disfigurement. In addition, nonevidence-based dietary restrictions, e.g. recommended by alternative medicine therapists, may lead to a further burden. Consequently, just counting the number of hives and rating of pruritus are not suitable ways to comprehend the full impact of chronic spontaneous urticaria on the patients. A better and more holistic approach is to measure the impairment of quality of life (QoL). This is why leading health authorities have strongly encouraged researchers to use QoL measurements and other patient-reported outcomes as major outcome parameters in pharmacological and other clinical trials (40). In addition, the importance of QoL assessment in urticaria is also stressed by the current EAACI/GA²LEN/EDF/WAO guidelines (41). Health-related QoL comprises different dimensions that impact the subjective well-being. Conversely, impairment of QoL is a good measure for the impairment and restrictions that patients generally experience because of their disease.

One of the pioneer works on QoL impairment in chronic spontaneous urticaria was performed by O'Donnell and colleagues. Using the well-established Nottingham Health Profile, they were able to demonstrate that chronic spontaneous urticaria patients suffer in many aspects a comparable QoL impairment as patients with severe coronary artery disease waiting for bypass surgery (42). They found many facets of everyday life to be affected including home management, personal care, recreation and social interaction, mobility, emotional factors, sleep, rest and work. Asked for the worst aspects of their disease, the patients stated the swellings, itch, pain, and feelings of being tired, irritable, weak or a feeling of loss of control over their lives. In addition, the unpredictability of the attacks, social restrictions, feeling embarrassed, time of work, restrictions of food or clothing, side-effects of drugs and being unable to relax or sit were mentioned (42). Disease severity was identified as a major driver of QoL impairment (2, 26). In addition, age and sex were demonstrated to have an impact on some dimensions of QoL (26), and ASST-positive patients were found to suffer from a more pronounced QoL reduction when compared to ASST-negative subjects (28). In summary, the results convincingly showed that patients do not suffer solely from physical problems but also from impairment in their daily activities, social life and emotional and mental well-being. During the last 10 years, many other publications confirmed the extent as well as the pattern of QoL impairment in chronic spontaneous urticaria patients (26, 43–46). In comparison with other skin diseases, chronic spontaneous urticaria was repeatedly shown to belong to the diseases with the strongest QoL reduction (47). Recently, a disease-specific instrument to assess QoL (chronic urticaria quality-of-life questionnaire – CU-Q2oL) has been developed (26, 48). The use of this instrument has lead to the identification and characterization of major drivers of QoL impairment in patients with chronic spontaneous urticaria, and it allows for monitoring the extent and

changes of their QoL both in clinical practice and in controlled trials.

The detrimental effect of chronic spontaneous urticaria on quality of life is greater than that of most other skin diseases and similar to that of severe coronary artery disease

Sleep deprivation

Of the symptoms of chronic spontaneous urticaria, pruritus is the most bothersome during the evening and at night when it makes falling asleep difficult and wakes patients later in the night (42, 44, 49, 50). These disturbances in sleep lead to chronic fatigue with a direct impact on QoL and physical and emotional well-being. As a consequence, productivity and performance at work are reduced and private and social life compromised. It has also been suggested that chronic pruritus with consequential sleep disturbances may also cause psychiatric comorbidity such as depression (51). Interestingly, chronic spontaneous urticaria patients who feel depressed have been found to suffer from particularly intense pruritus (49, 52), and pruritus severity is correlated to the extent of depression (52).

The majority of patients with chronic spontaneous urticaria suffer from sleep deprivation and a consequential reduction in quality of life

Psychiatric comorbidity

Patients with chronic spontaneous urticaria frequently exhibit psychiatric comorbidities with every second to every third patient seeming to be affected (45, 53, 54). Anxiety, depression and somatoform disorders are the most common associated psychiatric diseases. While disease activity and severity of chronic spontaneous urticaria do not seem to be correlated with the occurrence of psychiatric diseases (54, 55), QoL has been shown to be more reduced in urticaria patients who exhibit a concomitant psychiatric diagnosis when compared to patients who do not (45, 56). As yet, there is no evidence pointing at a causal relationship between chronic spontaneous urticaria and psychiatric disorders, and the data available do not support the notion of higher rates of psychiatric comorbidities in chronic spontaneous urticaria when compared to other chronic inflammatory skin disorders. For example, anxiety is also often encountered in patients with atopic dermatitis or food allergy because the uncertainty about when a new outbreak occurs is a feeling that is difficult to cope with. It thus seems obvious to all treating physicians that the fear of an unexpected flare up of chronic spontaneous urticaria has an especially strong psychological impact on patients. However, evidence for a true influence of a person's psychological profile on the cause or severity of chronic spontaneous urticaria is lacking. Future studies further examining this issue are strongly recommended. In any case, physicians should be aware of the fact that psychiatric comorbidity is not uncommon in chronic spontaneous urticaria patients and

that it may influence illness and help-seeking behaviour. It is, therefore, of paramount importance to recognize the psychiatric disorders and to take appropriate measures if present.

Many patients with chronic spontaneous urticaria exhibit psychiatric comorbidities, most commonly anxiety, depression, which should be taken into account in patient management

Socioeconomic impact

Perhaps the easiest way to assess the impact of chronic spontaneous urticaria on society is to measure its financial impact. The majority of patients need continuous medication to control the symptoms. Furthermore, many patients require regular or unanticipated health care visits (25), particularly those with angioedema who are seen frequently in emergency departments. Apart from direct costs for medication, laboratory analyses and costs of health care visits, the indirect costs resulting from the absence from work or reduced efficiency while at work must all be taken into consideration. Recently, DeLong and co-workers (57) were able to demonstrate that the mean annual total costs of chronic spontaneous urticaria patients conventionally treated with antihistamines are > \$2000 per patient per year. In this calculation, the authors included four direct and two indirect health care costs; medication, outpatient visits, hospital and emergency department visits, laboratory costs as well as wages lost because of travel to outpatient visits and wages lost because of absences from work. In addition, they found that 30% of patients required at least one hospital and emergency department visit per year, whereas 16% required two or more. Although, DeLong and colleagues studied the situation in a tertiary referral centre, the distribution of disease severity was not particularly high in the population studied (38% mild, 42% moderate, 20% severe). If the costs reported by DeLong et al. are recalculated based on the point prevalence of chronic spontaneous urticaria of around 0.5% to 1%, the total annual costs for chronic spontaneous urticaria would reach around \$2 500 000 000–5 000 000 000 in the USA. Another costing study was performed in 2002 in Europe using placebo data from clinical trials (58). In this report, direct and indirect costs amounted to a total of €2128 per patient per year which, assuming a population of 500 million, means an annual cost to the European community of between 5 000 000 000 and 10 000 000 000 Euros. It should be emphasized that these figures are mean values, and the costs of severely debilitated patients requiring more medical attention and expensive therapies may be much higher. As there are big differences in the health care systems between different countries and regions, it may not be possible to extrapolate these data from one country or region to another.

Chronic spontaneous urticaria has a large impact on the society in terms of direct and indirect health care costs as well as reduced performance at work and in private life

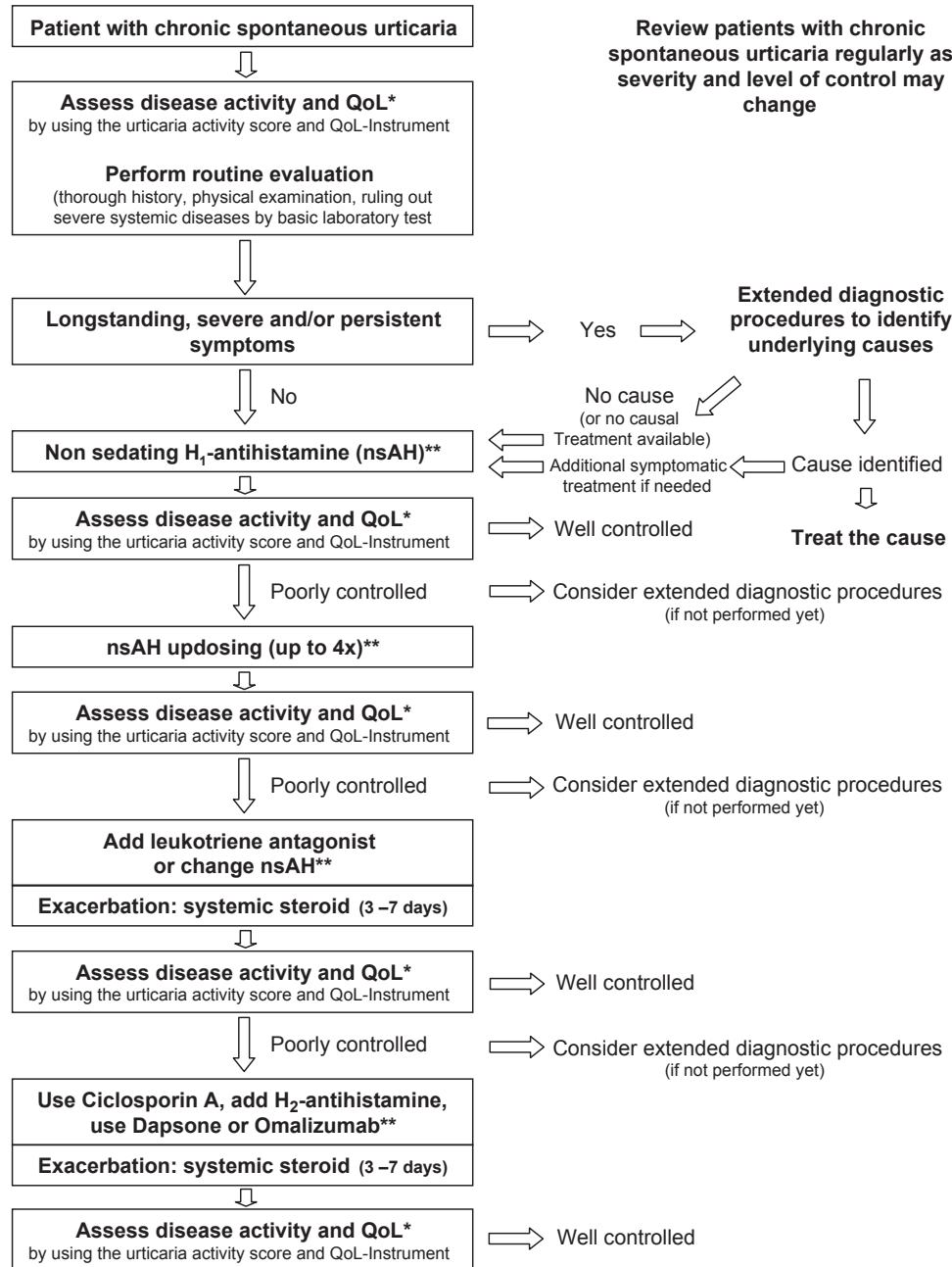
Treatment of chronic spontaneous urticaria

A two-pronged approach to management of chronic spontaneous urticaria has been suggested. The first is the attempt to identify and eliminate the underlying cause(s) and/or the eliciting trigger(s). The second is pharmacotherapy aimed at providing symptom relief. While eliminating the cause is the most desirable option, this seems to be not applicable in many cases. Currently, an intensive diagnostic programme is

recommended particularly for patients who suffer from long-standing and severe urticaria (Fig. 1). Of all diagnostic procedures, a thorough history is regarded as most important (1).

How often can chronic spontaneous urticaria be cured

To cure urticaria, its cause or trigger factors should be identified and eliminated. How often can this be carried out in chronic spontaneous urticaria? Many studies have addressed



*Quality of life (QoL)

**Based on the treatment algorithm of chronic spontaneous urticaria published in the current guidelines (41)

Figure 1 Flowchart for the management of patients with chronic spontaneous urticaria.

Table 4 Frequency of successful identification of underlying causes in selected patients with chronic spontaneous urticaria

Study	Country	<i>n</i>	Identification of underlying cause	Autologous serum skin test performed	Autoreactivity included in underlying causes
Small et al. (1982)	Canada	215	In 11% of patients	No	NR
Quaranta et al. (1989)	USA	86	In 0% of patients	No	NR
Humphreys and Hunter (1997)	UK	331	In 17% of patients	No	NR
Gimenez-Arnau et al. (2004)	Spain	235	In 43% of patients	In 92 patients	Yes
Kulthanan et al. (2007)	Thailand	407	In 17% of patients	In 61 patients	No
Ferrer (2009)	Spain	248	In 15% of patients	In 3 patients	NR

n, number of patients; NR, not reported.

this question in nonacute urticaria and report the finding of possible causes in only around 15–30% of patients (11–13, 15, 25, 59). But care must be taken in interpreting these results. Most authors examined patients with both chronic spontaneous urticaria and patients with physical urticaria and did not distinguish between them. When only looking at the data on patients suffering from chronic spontaneous urticaria, a successful identification of possible underlying causes varied from 0% to 43% of patients in different studies (12, 13, 15, 16, 24, 25) (Table 4). A further limitation of the data is that the data in these studies were generated at different times and by different patterns (type and number) of applied measures. Thus, it can be concluded from the available published data that a cause of chronic spontaneous urticaria is difficult to find and a causal and/or curative treatment is rarely available for the majority of patients. The current guidelines (1) suggest extended diagnostics aimed at the identification of underlying causes in patients who suffer from long-standing and/or severe chronic spontaneous urticaria. In our experience, many of these patients are referred to specialized centres, where a broader spectrum of investigation procedures can be applied. This may increase the success of identifying the causes of chronic spontaneous urticaria in individual patients.

In many patients, the causes and/or triggers of chronic spontaneous urticaria are not identified. Therefore, a causal and/or curative treatment is not available for a large number of patients

How effective are the currently approved symptomatic therapies

The current guidelines on the management of urticaria patients recommend aiming for a complete symptom relief (41). Symptomatic therapy with H₁-antihistamines, the only approved medication for chronic spontaneous urticaria, is the mainstay of treatment for the vast majority of patients. The first generation of these drugs has major side-effects, such as sedation and anticholinergic effects, and should not be used in the treatment of urticaria today (41, 60). Instead, the modern nonsedating H₁-antihistamines are well tolerated by most patients and recommended as first-line treatment (41). Their efficacy has been convincingly shown in many clinical studies.

However, many patients do not respond sufficiently to the approved doses. In this case, the current guidelines suggest an up dosing of the H₁-antihistamine up to fourfold. Both clinical experience and clinical studies support this approach with higher doses of H₁-antihistamines showing a higher efficacy in many, but not all, patients (61–64). In all patients who do not respond satisfactorily to H₁-antihistamines in high doses, the guidelines suggest to add a leukotriene antagonist or to change the H₁-antihistamine. In case this treatment regimen is not successful, other treatment approaches should be considered, such as ciclosporin, a combination of H₁- and H₂-antihistamines, dapsone or omalizumab (41) (Fig. 1). For most of the latter options, controlled studies have been performed, even though larger studies are needed. Currently, the best-quality evidence is available for ciclosporin (65, 66). Especially during the past 3 years, a growing body of evidence suggests a remarkable reduction in urticaria symptoms by omalizumab, with many patients becoming completely free of symptoms (67–71). It is important to assess all patients for the benefits and adverse effects of any therapy initiated. Also, patient compliance should be monitored.

From clinical experience, three groups of chronic spontaneous urticaria patients can be distinguished: (i) responders to the currently approved dosages of H₁-antihistamines, (ii) nonresponder to the currently approved dosages but responders to higher doses of H₁-antihistamines and (iii) nonresponder to H₁-antihistamines whatever dosage is applied (61). These three groups do not necessarily only relate to different patients but also to different periods of the disease in the same patient. The fact that these different patterns of response to H₁-antihistamines exist is also mirrored by the current treatment recommendations (41), which suggest a stepwise intensification of therapy in nonresponding patients. However, the proportion of patients who does not respond sufficiently to H₁-antihistamines is not well characterized. One reason is that most studies only look at the mean reduction in symptoms, but do not publish the number of responding patients. To address this issue, we performed a PubMed search on therapy with H₁-antihistamines in chronic spontaneous urticaria. The search words included 'Urticaria' and 'Antihistamine'. The only limit set was 'Randomized, Controlled Trial' in the section 'Type of Article'. Non-English publications, trials of before 1995, studies with mixed urticaria populations (e.g. acute and chronic spontaneous

Table 5 Studies reporting responder rates to treatment with antihistamines

Study	n	Treatment	Complete responder	Marked responder
Zhang et al. (2009)	132	Levamisole 50 mg + AH* (A) vs AH* plus PL (B)	37% (A) vs 16% (B)	76% (A) vs 54% (B)
Gimenez-Arnu et al. (2009)	538	AH† (A) vs rupatadine 20 mg (B) vs PL	NR	35% (A) vs 48% (B) vs 14% (PL)
Potter et al. (2009)	886	AH* (A) vs AH‡ (B)	NR	NR
Engin et al. (2008)	81	Narrow-band UVB plus AH* (A) vs AH* (B)	NR	NR
Grob et al. (2008)	142	AH‡ vs PL	NR	NR
Khalaf et al. (2008)	64	AH‡ + dipyrindamol 25 mg thrice daily (A) vs AH‡ + PL (B)	62% (A) vs 47% (B)	85% (A) vs 70% (B)
Dubertret et al. (2007)	283	Rupatadine 5 mg (A) vs AH† (B) vs rupatadine 20 mg (C) vs PL	NR	~55% (A) vs ~ 55% (B) vs ~70% (C) vs ~25% (PL)
Gimenez-Arnu et al. (2007)	334	AH† (A) vs rupatadine 20 mg (B) vs PL	NR	66% (A) vs 73% (B) vs 46% (PL)
Spector et al. (2007)	254	AH§ (A) vs PL	NR	NR
Ortonne et al. (2007)	142	AH‡ (A) vs PL	NR	69% (A) vs 37% (PL)
Pons-Guiraud et al. (2006)	192	Emedastine 2 mg twice daily (A) vs AH¶ (B)	NR	65% (A) vs 66% (B) (Inv. Eval.); 61% (A) vs 65% (B) (Pat. Eval.)
Godse (2006)	20	Montelukast 10 m (A) vs AH** (B)	NR	NR
Kapp and Pichler (2006)	166	AH* (A) vs PL	NR	52% (A) vs 27% (PL)
Nettis et al. (2006)	106	AH* (A) vs PL	53% (A) vs 0% (PL)	NR
Kaplan et al. (2005)	259	AH§ (A) vs PL	13% (A) vs 9% (PL) (Inv. Eval.); 12% (A) vs 7% (PL) (Pat. Eval.)	68% (A) vs 37% (PL) (Inv. Eval.); 70% (A) vs 34% (PL) (Pat. Eval.)
Di Lorenzo et al. (2004)	160	AH‡ (A) vs AH‡ plus montelukast 10 mg (B) vs montelukast 10 mg (C) vs PL	NR	NR
Nettis et al. (2004)	81	AH‡ (A) vs AH‡ plus montelukast 10 mg (B) vs PL	16% (A) vs 73% (B)	NR
Handa et al. (2004)	116	AH** (A) vs AH§ (B)	52% (A) vs 4% (B)	88% (A) vs 47% (B)
Monroe et al. (2003)	226	AH‡ (A) vs PL	NR	NR
La Rosa et al. (2001)	62	AH†† (A) vs oxatamide 2 mg (B)	NR	87% (A) vs 90% (B)
Camarasa et al. (2001)	55	AH‡‡ (A) vs AH§§ (B) vs PL	NR	56% (A) vs 47% (B) vs 11% (PL)
Ring et al. (2001)	190	AH‡ (A) vs PL	NR	NR
Nelson et al. (2000)	468	Fexofenadine bid: 20 mg (A) vs 60 mg (B) vs 120 mg (C) vs 240 mg (D) vs PL	NR	NR
Leynadier et al. (2000)	61	AH¶¶ (A) vs AH¶ (B)	50% (A) vs 46% (B)	NR
Finn et al. (1999)	476	Fexofenadine bid: 20 mg (A) vs 60 mg (B) vs 120 mg (C) vs 240 mg (D) vs PL	NR	NR
Dubertret et al. (1999)	247	AH¶¶ (A) vs AH¶ (B) vs PL	NR	NR
Breneman (1996)	188	AH** (A) vs hydroxyzine 10 mg (B) vs PL	NR	NR
Brostoff et al. (1996)	56	AH¶¶ (A) vs PL	NR	71% (A) vs 29% (PL)
Breneman et al. (1995)	187	AH** (A) vs astemizole 10 mg (B) vs PL	30% (A) vs 25% (B) vs 11% (PL)	75% (A) vs 61% (B) vs 47% (PL)

This is a shortened table. The full table can be found as Supporting Information. Results for antihistamines in standard dose are printed in bold.

n, number of randomized patients; NR, not reported; AH, standard dosed antihistamine; PL, placebo; A,B,C,D, treatment group A, B, C, D; Inv. Eval., investigators evaluation; Pat. Eval., patients evaluation.

*Levocetirizine 5 mg; †rupatadine 10 mg; ‡desloratadine 5 mg; §fexofenadine 180 mg; ¶loratadine 10 mg; **cetirizine 10 mg; ††cetirizine 5 mg (in preschool children); ‡‡azelastine 4 mg; §§sebastine 10 mg; ¶¶mizolastine 10 mg.

urticaria, physical and chronic spontaneous urticaria) and works including only highly selected populations such as difficult-to-treat patients were excluded. After ordering all suitable studies, a hand search was performed on responder rates. The results are presented in Table 5. In total, we identified 29 randomized controlled studies on the effect of H₁-antihistamines in chronic spontaneous urticaria (62, 72–99). Of these studies, only 18 report responder rates. In summary, most of the published results indicate that half or even less of the patients suffering from chronic spontaneous urticaria respond with a complete control of symptoms to licensed doses of H₁-antihistamines. In addition, around every third to every second patient does not respond with a marked improvement. It is important to emphasize that this analysis does not allow a comparison of the efficacy of different H₁-antihistamines, because the different authors did apply different approaches and examined different patient populations with different disease severities.

In general clinical practice, where therapy is often taken on an on-demand rather than on a regular basis (50), urticaria control can be expected to be even worse. Interestingly, a recent work also demonstrated that chronic spontaneous urticaria patients taking antihistamines continuously suffer from a significantly lower impairment of their QoL when compared to patients who do not (100).

The current standard therapy with regular dosed H₁-antihistamines leads to an absence of symptoms in <50% of patients with chronic spontaneous urticaria. Increasing the dose improves treatment responses but still every third to fourth patient will remain symptomatic

Conclusions

Chronic spontaneous urticaria is one of the most frequent skin diseases, and it is common for patients to suffer from it for many years. Poor sleep, mainly because of pruritus, and a reduced quality of life are experienced by the majority of patients, and the frequency of psychiatric comorbidities is high. Furthermore, not only does the disease have a major impact on patients but it also results in profound socioeconomic costs. Because an underlying cause is rarely detected, a causal and/or curative treatment is not available for the majority of patients. Therefore, symptomatic therapy remains the mainstay of treatment. Modern nonsedating antihistamines in licensed doses are the treatment of first choice. Currently, all other treatments are off-label. The aim of therapy should be a quick and complete symptom control. However, antihistamines are not sufficient in many patients. Alternative and approved therapeutic options are necessary to improve care for a large proportion of chronic spontaneous urticaria patients.

In summary, the following unmet needs of chronic spontaneous urticaria patients have to be addressed:

- The research on the epidemiology of urticaria in the general population should be intensified, e.g. to generate data on regional differences or data on special populations such as children.

- The research on the natural course of chronic spontaneous urticaria should be intensified.
- The question whether angioedema as an isolated symptom can be regarded as a subgroup of chronic spontaneous urticaria has to be answered.
- The resources allocated to diagnose and treat chronic spontaneous urticaria patients should be adequate, and the research into socioeconomic implications needs to be extended.
- The research for underlying causes in chronic spontaneous urticaria as well as in inducible forms of urticaria and their treatment should be intensified.
- More effective and safe therapies should be investigated for patients who do not respond to H₁-antihistamines.
- Research on compliance of chronic spontaneous urticaria patients and reason for noncompliance should be performed for guideline-recommended treatment options.

Generation of this GA²LEN task force report

This report is the outcome of a GA²LEN task force implemented by the GA²LEN executive committee to identify and characterize unmet clinical needs in urticaria. In a first step, a thorough literature research was performed on the epidemiology, course and impact of the disease as well as on the efficacy of nonsedating antihistamines. Subsequently, the results were verified and/or corrected according to the experience and unpublished data from participating and other centres. Based on this information, Marcus Maurer, Karsten Weller and Torsten Zuberbier prepared a first draft version of the report. This first draft was then circulated to all participating centres and revised according to their corrections, comments and suggestions. During a consensus meeting in London in June 2010, the revised draft was discussed extensively with the representatives of the participating centres. Based on this discussion, the manuscript was revised for a second time. All authors then again reviewed, completed or changed the manuscript and sent it back to the first authors. After a prefinal version was composed out of all of the changes, and a final review and approval was obtained from all contributing authors, the final version of the manuscript was submitted.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at www.wileyonlinelibrary.com

Table S5. Studies reporting responder rates to treatment with antihistamines (full version)

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