

REVIEW ARTICLE

Questions and answers in chronic urticaria: where do we stand and where do we go?

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Abstract

This supplement reports proceedings of the second international Global Urticaria Forum, which was held in Berlin, Germany in November 2015. In 2011, a report of the GA²LEN task force on urticaria outlined important and unanswered questions in chronic urticaria (CU). These included, but were not limited to, questions on the epidemiology and course of chronic spontaneous urticaria (CSU) [also called chronic idiopathic urticaria (CIU)], the resources allocated for the diagnosis and treatment of CSU, whether patients with angioedema as an isolated symptom can be regarded as a subgroup of CSU, and the efficacy and long-term safety of therapies. Many of these questions have been addressed by recent studies. Some of the answers obtained raise new questions. Here, we summarize some of the key insights on CU obtained over recent years, and we discuss old and new unmet needs and how to address them with future studies. We need to analyze the influence of recent advances in understanding of the burden of CU on patients and society, disease management and the CU patient journey. Our increased understanding of urticarial pathophysiology and consideration of the patient as a whole will need to be translated to better treatment algorithms and protocols. Actions to address these challenges include the 5th International Consensus Meeting on Urticaria, which will take place later this year. The formation of a global network of Urticaria Centers of Reference and Excellence over the next few years has also been proposed, with the aim of providing consistent excellence in urticaria management and a clear referral route, furthering knowledge of urticaria through additional research and educating/promoting awareness of urticaria.

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Conflicts of interest

- Marcus Maurer is, or was recently, a speaker and/or advisor for FAES, Almirall Hermal, Genentech, GSK, Merckle Recordati, Novartis, Sanofi-Aventis, MSD, Moxie, Takeda, Shire, UCB and Uriach.
- Martin Church has been a speaker or consultant for Almirall, FAES Pharma, Menarini, Moxie, MSD, Novartis, UCB Pharma, Sanofi-Aventis and Uriach.
- Alexander Marsland has acted as a speaker and/or advisor for Galderma, GSK, Novartis and UCB Pharma.
- Gordon Sussman has recently acted as a consultant and speaker for Novartis, Merck, CSL Behring, Pfizer and Shire.
- Frank Siebenhaar is, or was recently, a speaker or advisor for Abbott, Braun, Dr. Pflieger, Moxie, Novartis, Patara Pharma, Procter & Gamble and Uriach.
- Christian Vestergaard has acted as a speaker for Novartis, Abbvie, LEO Pharma, and served on advisory boards for Novartis, Abbvie and Sanofi.
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Burden and patient journey in chronic spontaneous urticaria – Where do we stand?

The burden of chronic urticaria (CU) on patients and their use of healthcare resources have been investigated in several studies.^{1–4} Recently, the multinational, real-world ASSURE-CSU/CIU (Assessment of the Economic and Humanistic Burden of Chronic Spontaneous/Idiopathic Urticaria Patients) study examined the burden of disease in 673 CSU patients whose disease had persisted for >12 months and who were symptomatic despite treatment.^{5,6} Patients were recruited from 64 specialist centers/hospitals in seven countries and treating physicians were mostly dermatologists, allergists and urticaria specialists.^{5,6}

The study included a retrospective medical chart review in conjunction with patient surveys (including validated tools for the assessment of disease impact) and a patient diary. The primary objectives were to describe patient demographics, medical history, treatments and healthcare resource utilization based on medical record data, and to assess the socioeconomic impact of CSU.^{5,6}

In line with other epidemiological studies, the majority of patients included in ASSURE-CSU were female (72.7%). Most of the study population was of Caucasian/white ethnicity (90.4%). When patients were included, they already had a mean diagnosed disease duration of almost 5 years (57.1 months) and the majority of patients had experienced symptoms for 2 years before diagnosis.⁶ Mean age was 42 years at CSU symptom onset, 44 years at diagnosis and 48 years at enrolment in ASSURE-CSU.⁶ Disease duration and the unexpectedly long time from symptom onset to diagnosis demonstrate the significant burden of CSU on patients and healthcare systems as a result of the suboptimal patient journey.

The EAACI/GA²LEN/EDF/WAO urticaria guideline recommends assessing CSU disease activity with the 7-day Urticaria Activity Score (UAS7).⁷ A UAS7 of 0 represents no urticaria symptoms. A score of 1–6 typically represents well controlled disease, 7–15 indicates mild urticaria, 16–27 indicates moderate urticaria and UAS7 of 28–42 generally indicates high urticaria activity.⁸ In the overall study population, the majority of patients had moderate to high CSU activity at diagnosis (11.2% mild, 31.4% moderate, 36.5% high disease activity, data missing for 21%).⁶ The mean UAS7 score was 17.3, indicating moderate to high disease activity. Disease activity was assessed by physicians using a range of criteria/tools, but validated patient-reported outcomes tools (UAS7) were used in very few cases.⁶ Criteria most used by physicians to assess disease activity included number of flares, impact on quality of life and medication requirements.⁶

Perhaps surprisingly, CSU-associated angioedema was reported by over half of all patients (58.5%) with a mean of 19 angioedema episodes occurring per patient per year.⁶ The presence of angioedema therefore may previously have been generally

Table 1 Where do we stand and where do we go in chronic urticaria?

Where do we stand?	Where do we go?
The presence of angioedema in CSU may previously have been generally underestimated	Further study of the classification of angioedema to ensure occurrences are reported using the same criteria
In patients who remain symptomatic to second-line treatment, the EAACI/GA ² LEN/EDF/WAO urticaria guideline recommends add-on omalizumab or ciclosporin or montelukast	Third-line treatment order to be discussed, with consensus needed
Patients who respond to omalizumab can be fast (by 4–6 weeks) or slow (by 12–16 weeks) responders	Clarification of omalizumab response patterns and how these impact treatment management (dose, dose intervals, treatment duration)
In patient case studies, omalizumab is effective in reducing urticaria symptoms in patients with CIndU	More research regarding omalizumab in the treatment of CIndUs
Physicians have described significantly raised levels of emotional distress and mental disorders in CSU	Need for properly structured studies that incorporate the whole person approach into standard drug therapy regimens
Much heterogeneity still exists in the treatment of urticaria globally	Need for centers of reference and increased adherence to the EAACI/GA ² LEN/EDF/WAO urticaria guideline

CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; EAACI, European Academy for Allergy and Clinical Immunology; EDF, European Dermatology Forum; GA²LEN, Global Allergy and Asthma European Network; WAO, World Allergy Organization.

underestimated, although a clearer definition is needed for angioedema, vs. a large hive or other swelling (Table 1). Further study of the classification of angioedema is required to ensure physicians (and patients in self-reported studies) are reporting occurrences using the same criteria. It is interesting to note that the rate of occurrence of angioedema varied greatly between countries participating in the study. For example the rate at diagnosis was 53% in the UK, but only 41% and 19% in Canada and Germany, respectively, perhaps demonstrating a lack of consistency in diagnosing angioedema.⁹

The EAACI/GA²LEN/EDF/WAO urticaria guideline recommends only very limited routine diagnostic measures in CSU, with an extended diagnostic programme to be used only where indicated, based on patient history and suspected cause.⁷ Results from the ASSURE-CSU study showed that diagnostic testing for triggers was performed in 75.1% of patients.⁶ Some physicians test for autoreactivity, because they believe a positive test may indicate higher disease activity and predict longer duration. Patients with a positive test for autoreactivity may also ‘stop looking’ for other underlying causes and be reassured of a

sufficient explanation for their CSU. The two tests used to look for autoreactivity are the autologous serum skin test (ASST) and the basophil histamine release assay (BHRA). These tests indicate the presence of histamine-releasing serum factors such as autoantibodies against either immunoglobulin E (IgE) or high affinity Fc receptors (FcεRI) that are believed to be pathogenic in up to 40% of patients with CSU.¹⁰ It should be noted that these tests are neither sensitive nor specific for urticaria. The presence of other types of histamine-releasing or mast cell-activating factors may also lead to a positive result with the ASST or BHRA. The general experience among physicians is that healthy controls and patients without CSU do not have positive ASST responses, as defined by an inflammatory red hive response.⁷ The ASST is a relatively laborious/time consuming test to perform, and some clinicians prefer to use the BHRA.¹¹ The value of a positive test for autoreactivity in terms of changing management has not yet been demonstrated, although patients with positive BHRA may respond better to ciclosporin than BHRA-negative patients.¹² In contrast, patients who are BHRA negative may respond better to omalizumab than patients who are BHRA positive.¹³

In accordance with guideline-recommended first- and second-line treatment for CSU,⁷ second generation H₁-antihistamines are expected to be the most frequently used therapy, either alone or in combination with other treatments. It is important to note that ASSURE-CSU study data were predominantly collected across a time period prior to the licensing of omalizumab for the treatment of CSU. Other treatments commonly used during this time were leukotriene receptor antagonists (LTRAs), oral corticosteroids, first generation H₁-antihistamines, H₂-antihistamines, ciclosporin and other immunosuppressants. Variation in drug use from country to country reflects different clinical approaches as well as differing availability of drugs. Similarly, the practice of combining treatments may vary from country to country, with some countries much more likely to do this than others.

Outside of the ASSURE-CSU study, the rate of adherence to the international urticaria guideline was found to be as low as 11% among primary care practitioners. It was found that there were differences in prescribing patterns before and after review at a specialist clinic. After specialist review, data indicate an increase in international urticaria guideline adherence. Non-sedating antihistamines were the main pillar of CU treatment and were used in 67% of cases. The application of guideline-based management following specialist review was associated with a good outcome in 78% of patients with CU.¹⁴ A survey in Germany found that among private dermatologists, pediatricians and general practitioners, the diagnosis and management of patients with urticaria was only partially in accordance with the EAACI/GA²LEN/EDF/WAO guideline on urticaria and the general level of implementation of the guideline was low.² The majority of specialist centers have

been shown to follow the guideline by using licensed doses of non-sedating H₁-antihistamines as first-line treatment (71%) and up dosing of H₁-antihistamines as second-line treatment (61%).¹ Since the licensing of omalizumab for the treatment of urticaria, treatment practices have changed, reflecting increasing evidence for therapies that are beneficial in the management of patients with CSU. As of 31 December 2014, cumulative exposure to omalizumab for patients with CSU is estimated to be 17 008 patient-treatment-years.¹⁵ The update and revision of the international EAACI/GA²LEN/EDF/WAO guideline on urticaria regarding the treatment of CSU, as well as its diagnosis and classification, may further decrease the heterogeneity in treatment practice and thereby reduce the burden of disease identified by the ASSURE-CSU study (Table 1).

Diagnosis and classification of urticaria – What we know and what we need to know

Results from the ASSURE-CSU study showed that it can take on average 2 years before a patient receives a correct CSU diagnosis from an urticaria specialist.⁶ The EAACI/GA²LEN/EDF/WAO urticaria guideline is nevertheless very detailed, with clear guidance on how to make a diagnosis of CSU. Urticaria, which manifests as hives (wheals), angioedema, or both (Fig. 1), may be classified into subtypes based on the duration of the condition since its onset (chronic or acute) and the presence or absence of

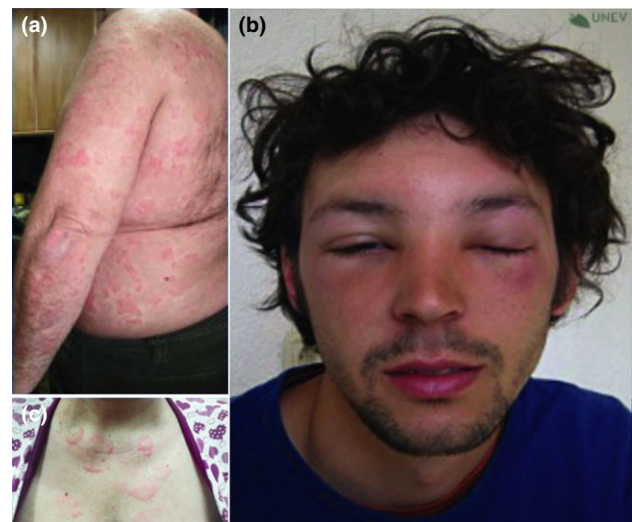
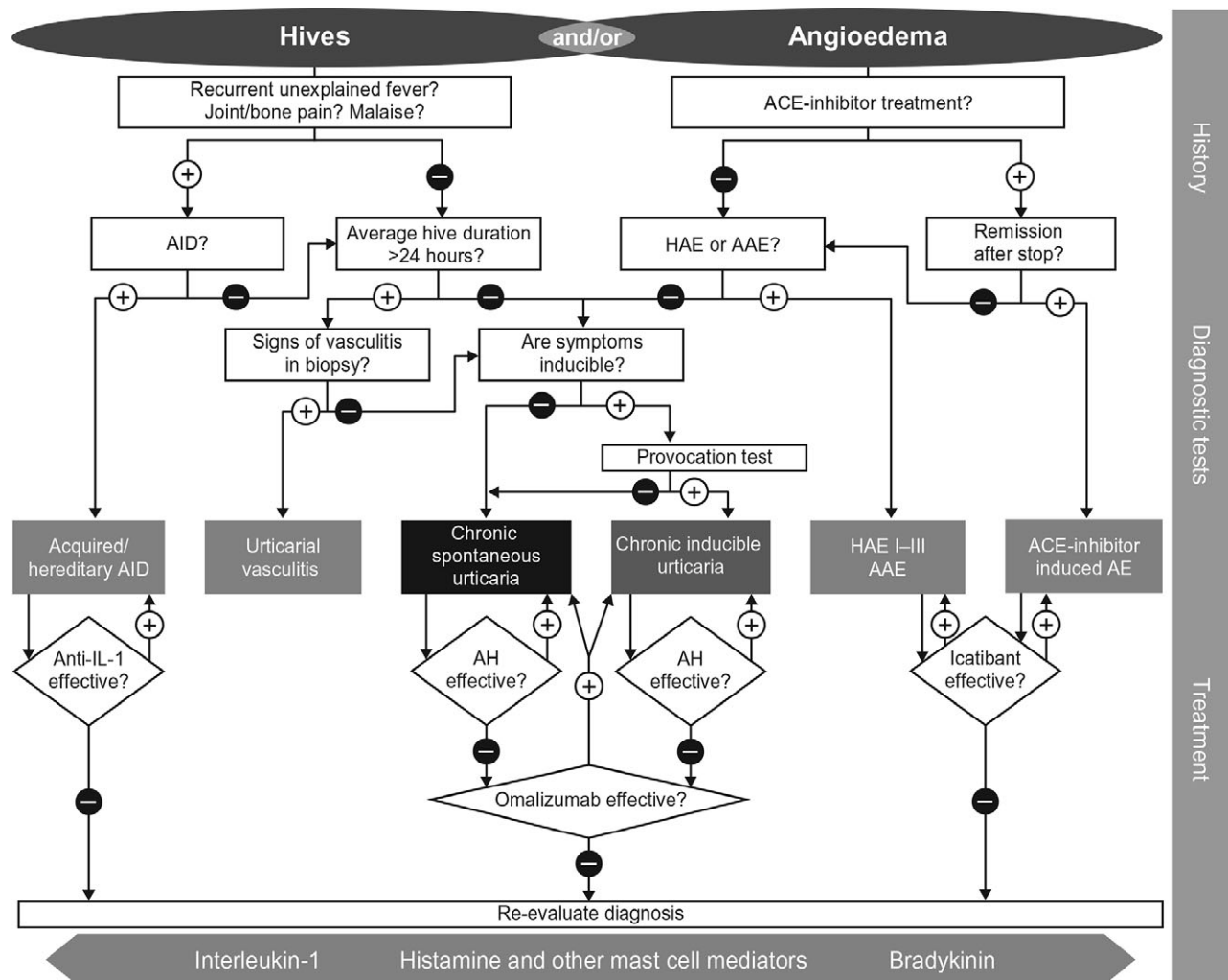


Figure 1 Symptoms of urticaria. (a) Hives – central swellings of variable size, often surrounded by reflex erythema. Associated with itching; individual hives usually resolve within 1–24 h; (b) Angioedema – sudden, pronounced erythematous or skin coloured swelling of the lower dermis and subcutis with frequent involvement below mucous membranes. Sometimes associated with pain rather than itching; resolution can take up to 72 h. Photographs (a) courtesy of Novartis Pharma AG; (b) reproduced with kind permission from UNEV; patient consent received.

A thorough history should form the initial part of the diagnosis, and should include a variety of questions relating to potential causative factors and distinguishing clinical symptoms. The



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1. Time of onset of disease
2. Frequency/duration of and provoking factors for hives
3. Diurnal variation
4. Occurrence in relation to weekends, holidays, and foreign travel
5. Shape, size, and distribution of hives
6. Associated angioedema
7. Associated subjective symptoms of lesions, for example itch, pain
8. Family and personal history regarding urticaria/atopy
9. Previous or current allergies, infections, internal diseases, or other possible causes
10. Psychosomatic and psychiatric diseases
11. Surgical implantations and events during surgery, for example after local anesthesia
12. Gastric/intestinal problems
13. Induction by physical agents or exercise
14. Use of drugs (e.g., non-steroidal anti-inflammatory drugs (NSAIDs), injections, immunizations, hormones, laxatives, suppositories, ear and eye drops, and alternative remedies)
15. Observed correlation to food
16. Relationship to the menstrual cycle
17. Smoking habits (especially use of perfumed tobacco products or cannabis)
18. Type of work
19. Hobbies
20. Stress (eustress and distress)
21. Quality of life related to urticaria and emotional impact
22. Previous therapy and response to therapy
23. Previous diagnostic procedures/results

Figure 3 EAACI/GA²LEN/EDF/WAO 2013 urticaria guideline-recommended key questions to ask as part of a thorough patient history.⁷ EAACI, European Academy for Allergy and Clinical Immunology; EDF, European Dermatology Forum; GA²LEN, Global Allergy and Asthma European Network; WAO, World Allergy Organization. Reproduced from Zuberbier *et al.* Allergy 2014;69(7):868–87. Copyright © 2014 Wiley, with permission.⁷

recommended questions to ask as part of a thorough medical history are shown in Fig. 3.⁷

Diagnostic testing should be guided by the patient history. Few routine diagnostic measures are recommended and extended testing should only be done in patients with long-standing and/or severe disease and based on patient history, for the identification of underlying causes or eliciting factors and for ruling out possible differential diagnoses (Fig. 4).⁷ Attendees at the Global Urticaria Forum (Berlin, Germany, November 2015) reported some variation in which tests they as physicians routinely use and, as observed with ASST, certain tests were not available in all countries.

Some patients may have 'urticaria-like' rashes that are not urticaria. It is very important that physicians accurately diagnose urticaria to optimize treatment outcomes. Incorrect diagnosis is one reason for poor response to treatment and therefore sub-optimal treatment choice. Differential diagnoses of urticaria range from acquired or hereditary autoinflammatory disorders and urticarial vasculitis in patients with hives to hereditary angioedema (HAE), acquired angioedema due to C1-inhibitor deficiency (AAE) and angiotensin-converting enzyme (ACE) inhibitor-induced angioedema in patients with angioedema (Fig. 2).⁷ In patients with hives alone together with fever, joint/bone pain or general malaise, the physician should consider and exclude autoinflammatory disease or urticarial vasculitis as alternative diagnoses. In patients whose hives tend to last for >24 h and leave bruising, a skin biopsy may be carried out to look for features of urticarial vasculitis (inflammatory cell infiltrate with evidence of focal vascular damage). It should be noted that while

Diagnostic tests		
	Routine	Extended*
Spontaneous	- Differential blood count - ESR or CRP - Omission of suspected drugs	- Infectious diseases - Type 1 allergy - Autoantibodies - Thyroid hormones - Skin tests - Pseudoallergen - Tryptase** - ASST - Skin lesion biopsy
CSU		
Inducible		
CIndU		
Cold	Cold provocation/threshold test	- Differential blood count and ESR or CRP - cryoproteins - Rule out other diseases especially infections
Delayed pressure	Pressure test/threshold test	None
Heat	Heat provocation/threshold test	None
Solar	UV and visible light of different wavelengths and threshold test	Rule out other light-induced dermatoses
Dermographic	Elicit dermatographism and threshold	None
Vibratory	Test with, for example, vortex	None
Cholinergic	Exercise and hot bath provocation	None
Aquagenic	Wet cloths at body temperature applied for 20 minutes	None

Figure 4 EAACI/GA²LEN/EDF/WAO 2013 urticaria guideline-recommended diagnostic tests.⁷ *Depending on suspected cause. **As indication of severe systemic disease.

ASST, autologous serum skin test; CIndU, chronic inducible urticaria; CRP, C-reactive protein; CSU, chronic spontaneous urticaria; EAACI, European Academy for Allergy and Clinical Immunology; EDF, European Dermatology Forum; ESR, erythrocyte sedimentation rate; GA²LEN, Global Allergy and Asthma European Network; WAO, World Allergy Organization. Reproduced from Zuberbier *et al.* Allergy 2014;69(7):868–87. Copyright © 2014 Wiley, with permission.⁷

a positive biopsy can confirm urticarial vasculitis, a negative one cannot necessarily exclude it.

If a patient has angioedema without hives and is taking an ACE inhibitor, and if symptoms subside following withdrawal of this treatment, then ACE inhibitor-induced angioedema is the most likely diagnosis. In those patients with angioedema alone who are not taking an ACE inhibitor, HAE or AAE, although rare, should be considered.

A provocation test should be carried out if CIndU is suspected from the history; that is if patients are able to 'make their hives appear', for example by scratching, or by exposure to cold (Fig. 4).⁷ In patients with CIndUs, the use of provocation tests, which can measure the threshold at which hives appear, is useful to be able to demonstrate to the patient the relevance of specific triggers and that their treatment is working. CIndU and CSU can occur concomitantly and CIndUs are seen most often in patients who also suffer from CSU. It is not known whether patients with CIndU have some differences in their skin that make them more receptive to provocation than other people.

This may be revealed with improved understanding of the pathophysiological mechanisms of urticaria.

Treatment of urticaria: insights from its pathophysiology

Mast cell degranulation and the release of histamine and other inflammatory molecules/mediators are thought to be central to the symptoms of urticaria. Consequently, guideline-recommended first- and second-line treatment is with non-sedating H₁-antihistamines.⁷ These are very effective in some patients, yet many still experience symptoms of urticaria, even with up to four times the licensed dose. The EAACI/GA²LEN/EDF/WAO urticaria guideline recommends add-on omalizumab, ciclosporin or montelukast third line for the treatment of chronic urticaria with an inadequate response to H₁-antihistamines (Table 1).⁷

In the pivotal randomized clinical trials ASTERIA I, ASTERIA II and GLACIAL, omalizumab, a monoclonal humanized recombinant IgG₁ antibody, demonstrated excellent efficacy and safety for the treatment of CSU.^{20–22} Interestingly, it has been noted that patients who respond to omalizumab can be fast (symptom response within 4–6 weeks week of treatment) or gradual responders (symptom response is slow over the course of approximately 12–16 weeks).²³ This may hint at the existence of several potential mechanisms of action operating at different rates.

In an analysis of response patterns from the phase III omalizumab CSU trials, at Week 4, a complete response (UAS7=0) was noted in 19%, 24% and 15% of patients receiving omalizumab 300 mg in ASTERIA I, ASTERIA II and GLACIAL, respectively. With continued omalizumab 300 mg treatment, 58.1% of patients in ASTERIA I and 48.9% of patients in GLACIAL, who had not met definitions of response at Week 12, met those definitions at Week 24.²³ A retrospective analysis of data from omalizumab-treated patients (20 with CSU, 21 with CIndU and 10 with both) demonstrated complete responses in 57% of patients within a week of treatment in 86% of patients within 4 weeks of treatment.²⁴ In addition, all 12 of the CSU patients who responded within a week, did so on the first day of treatment in this series.²⁴ In patients who received a single dose of omalizumab, the symptoms reappeared in most patients after 5 weeks.²⁵ This indicates that the presence of omalizumab is required to 'hold something in check' and relieve symptoms: it does not appear to cure the disease.

Activation of mast cells may occur through autoimmune, allergic or idiopathic mechanisms.^{26–28} Which of these mechanisms is relevant in individual patients with chronic urticaria is poorly understood, and efforts are underway to better understand this. The mechanisms of skin mast cell activation and their significance for individual patients and CSU sub-forms may become clearer when considered in the context of the activity of therapeutic agents and the clinical response to treatment with

these agents. Following administration via a subcutaneous injection, omalizumab diffuses into the blood stream and tissues, and it is thought that it may relieve the symptoms of CSU through different actions.

A proposed fast mechanism of omalizumab is its binding to the Cε3 domain of soluble IgE, which can then no longer bind to FcεRI on the surface of mast cells and basophils.^{29–31} Another fast mechanism is that complexes, trimers and hexamers, are formed between IgE and omalizumab, which may lead to a rapid sequestration of autoallergens and anti-IgE autoantibodies.^{29,30} This occurs mainly in the blood, but possibly also in the tissues.

A proposed slower mechanism is suggested in patients who have IgG antibodies capable of interacting with mast cell-bound IgE or its receptor, FcεRI.³² In this case, the reduction in mast cell and basophil bound IgE and subsequent down-regulation of the FcεRI receptor reduces its ability to be activated. Such down-regulation occurs gradually over the course of several weeks. More research is needed to determine if these potential fast and slower mechanisms of action for omalizumab can be related to the differing patterns of treatment response (Table 1).

In patient case studies, omalizumab is also effective in reducing urticaria symptoms in patients with CIndU.²⁴ The mechanisms of mast cell activation and action of omalizumab in CIndU remain unclear, but some authors propose that an autoallergic component is present in conjunction with symptom induction by physical stimuli. More research and controlled studies, on the efficacy and safety of omalizumab in these CU subtypes are needed (Table 1).

Treating the urticaria patient as a whole

To see urticaria as a purely pathophysiological process that happens to the skin is to fall short of understanding patients as whole persons. Assessing a patient's urticaria purely from the perspective of their clinical symptoms ignores a large and important part of their disease experience. Over the past century, a succession of reports has suggested a role for emotions and stress in initiating and perpetuating urticaria.³³ Recent psychoneuroimmunology research points to a significant influence of the 'mind-brain complex' on the immune system. Yet, it is still rare for psychological influences to be addressed by urticaria research.

Physicians have described significantly raised levels of emotional distress and mental disorders in CSU and have called for the screening of these elements in routine clinical care and for controlled clinical trials addressing the issue.^{34,35} However, such trials are very challenging to construct, making gathering evidence around this subject relatively problematic. The 2011 GA²LEN task force report noted the potential role of stress in precipitating and exacerbating CSU as well as the likelihood that CSU itself can act as an important cause of stress.¹⁶

As described in the non-dualistic 'mind-body' co-emergence model, it is important to recognize that the mind and body are not separate entities.³⁶ Each dimension may impact the other significantly, and allergists and dermatologists commonly acknowledge, at least informally, that in the clinic they recognize links between physical symptoms (hives and angioedema) and an urticaria patient's collateral life experience and emotions.

With all this in mind, physicians could be more open to incorporating body-and-mind, whole person assumptions, perspectives and approaches within their ordinary medical consultations, and to optimize their interpersonal interactions with patients. This way, important emotional elements are able to be noted and responded to in a way that facilitates overall treatment and wellbeing.

These elements can be included in ordinary consultations with patients.³⁷ It should be normal practice to ask questions that uncover the neglected 'mind', life experiences and stresses. Physicians can initiate consultations by telling their patients that they are interested in treating the whole person and that they would like to ask about both physical and non-physical elements of their disease if the patient is comfortable with that approach. It is useful to ask something like the following 'open' question to give the patient the opportunity to choose for themselves how to define their experience: 'What was the most interesting, memorable, significant, difficult, problematic, troublesome, hard, frustrating, stressful thing or things that happened around the time you first got your urticaria, or when it happened last?'³⁷

It can take time for a clinician to become competent in 'holding' together and integrating the normative biomedical approach with appropriate attention to the patient's 'story' and wider personhood.³⁸ It is helpful for physicians to listen warmly and with empathy, and to gently educate the patient regarding the possible mind/body connections ('perhaps stress is connected to your symptoms?'). This must be done without stigmatization or psychiatrization. Having established a safe encounter, the physician can suggest that the patient think a bit more about any possible connections and offer to follow-up with them soon. Many patients, once aware of a connection between their 'story' and their symptoms, will proactively change things in their lives, and get well using their own resources. Other patients may need specialized psychotherapy and can be referred, but only after trust has been established, and only to a professional who can address mind and body together.

ASSURE-CSU study results hint that patients may suffer from urticaria for many years without the emotional impact of their disease being recognized. Their mental and emotional health is as important as their physical symptoms; addressing feelings and ascribing meaning, encouraging patients to understand their feelings and where relevant make connections to life events can have a powerful impact on outcomes. Properly structured studies that incorporate the whole person approach into standard drug therapy regimens are needed (Table 1).

Heterogeneity in urticaria management and the emergence of urticaria centers of reference

Despite the availability of an international guideline, much heterogeneity still exists in the treatment of urticaria globally. Clinical decisions regarding the best diagnostic and therapeutic approaches can vary from one allergist or dermatologist to another and between clinical centers. The GA²LEN task force on urticaria highlighted that unmet needs are present in this area, for example the need to harmonize diagnostic and therapeutic approaches and to work more closely as an urticaria community, pooling collective experience.¹⁶ The global Chronic Urticaria Registry, CURE (www.urticaria-registry.com), is an initiative that aims to achieve this.

The urticaria clinic at the Department of Dermatology and Allergy at Charité – Universitätsmedizin Berlin is focused solely on treating patients with hives, angioedema or both and has dedicated physicians, researchers, research students, research assistants, technicians, study nurses and a study coordinator. As a result, in a structured setting, they have around 4500 patient contacts and are able to see 1800–2000 new urticaria patients every year. What is learned in a setting like this is very different to what can be learned by working alone in private practice, or a smaller hospital setting as a general dermatologist treating many different diseases, rather than focusing on one.

GA²LEN, the Global Allergy and Asthma European Network, created in 2004, is a unique network or consortium of 31 partners from top allergy institutions in their respective countries with the aim of decreasing the burden of allergy and asthma throughout Europe. There are 26 European members, as well as collaborating partners from outside Europe, and the network is still growing. GA²LEN recently gave a mandate to its urticaria task force to develop as a pilot project a 'Urticaria Center of Reference and Excellence Program'.³⁹

GA²LEN Urticaria Centers of Reference and Excellence (GA²LEN UCAREs) could help to harmonize the treatment of urticaria. It is important to note that, in practice, the international urticaria guideline is challenging to implement globally. As noted in the ASSURE-CSU study, different countries and regions have different frameworks, with different access to drugs and even different conceptions of the disease. Urticaria Centers of Reference and Excellence can be useful to address the heterogeneity that still exists (Table 1). It may also be helpful to have a hierarchy where less experienced doctors know where to refer for advice as well as for the treatment of difficult patients.

GA²LEN UCAREs will serve as referral centers providing excellence in urticaria management, increase the knowledge of urticaria by research and education and promote awareness of urticaria by advocacy activities. The interaction of GA²LEN UCAREs as a network will also help to increase urticaria knowledge and harmonize its management.

Infrastructure/setup

- Hospital setting
- Outpatient clinic with separate clinic hours for urticaria patients headed by expert
- Open to children and adult patients
- Team of dedicated staff, with specific urticaria training
- Multidisciplinary approach
- Accessibility and visibility
- Communication skills
- Quality management, structured and valid protocols of diagnosis and management
- Structured documentation, recording and archiving of patient data
- Critical incidence reporting and error management
- Assessment of patient satisfaction and unmet needs
- In team communication
- Active recruitment of research funding and support for educational activities and advocacy on urticaria
- Support of the UCARE network
- "Never give up" attitude

Management of urticaria

- Knowledge of and adherence to the EAACI/GA²LEN/EDF/WAO urticaria guideline
- Knowledge and use of current nomenclature and classification of urticaria
- Knowledge and use of guided history taking/anamnesis
- Knowledge and use of differential diagnostic algorithm
- Knowledge and use of standardized assessments and monitoring of disease activity, impact and control of disease
- Identification of comorbidities
- Provocation and threshold testing in CIndUs
- Knowledge and use of therapeutic algorithm
- Counseling

Clinical and basic research

- Scientific orientation
- Scientific activity
- Scientific productivity
- Clinical trials
- Participation in registry

Education

- Educational activities

Advocacy

- Increase awareness of urticaria
- Interaction with and support of patient organization(s)

Figure 5 The 32 requirements for a GA²LEN Urticaria Center of Reference and Excellence (UCARE).³⁹ CIndU, chronic inducible urticaria; EAACI, European Academy for Allergy and Clinical Immunology; EDF, European Dermatology Forum; GA²LEN, Global Allergy and Asthma European Network; WAO, World Allergy Organization.

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There are 32 requirements for a UCARE (Fig. 5), including factors relating to infrastructure and setup, management of urticaria, clinical and basic research, education and advocacy. These defined tasks should be fulfilled by the urticaria centre and will be tested in an audit by GA²LEN; part of the checklist they will use is shown in Fig. 6.

Departments are encouraged to apply to be a UCARE in their area, with the vision that by 2017 there will be a worldwide network of UCAREs. Every UCARE will automatically become part of the audit network and will be able to visit other centres to share knowledge and ultimately increase the extent of CSU research.

Summary

Many previously unmet needs in CU have been addressed by recent studies. We now understand better that urticaria impacts many aspects of patients' daily lives, with a considerable psychological and social burden and many patients suffering from anxiety and depression. New data show that a patient's journey through the healthcare system, from the onset of their CSU symptoms to diagnosis and treatment, can be a long one. A great deal of disease burden may be experienced by patients prior to them receiving a beneficial treatment. To optimize the patient journey, it is important to keep the time to diagnosis and treatment as short as possible by optimizing their management.

Infrastructure/Set-up			
Requirement	Explanation	Deliverable(s)	Yes/No
14. Support of the UCARE network	Training and activities in auditing and certifying GA ² LEN UCAREs and interaction with other UCAREs	Letter of intent to serve as a GA ² LEN UCARE auditor and to contribute to other UCARE network activities	☐ ☐
15. "Never give up" attitude	Staff needs to exhibit high motivation to help urticaria patients and show understanding that they may be the last resort of patients. Staff needs to convey to patients, that they are in good care and that the center will help them, however hard this may be.	Evidence of "never give up" - attitude by staff interview	☐ ☐

Management			
Requirement	Explanation	Deliverable(s)	Yes/No
1. Knowledge of and adherence to the EAACI/GA ² LEN/EDF/WAO urticaria guideline	All center staff members need to know the current version of the international EAACI/GA ² LEN/EDF/WAO guideline and their corresponding national guideline, if available. Center approach to urticaria needs to be based on guideline recommendations.	EAACI/GA ² LEN/EDF/WAO guideline is present (paper / electronic version) Center staff can answer questions on the urticaria guideline recommendations Center physicians can show, by use of a patient file, that management decision are based on guideline recommendations	☐ ☐ ☐ ☐ ☐ ☐
2. Knowledge and use of current nomenclature and classification of urticaria	Center staff needs to know and use the current urticaria classification and nomenclature	Evidence that staff use current urticaria nomenclature and classification*, e.g. by interview and/or patient file review	☐ ☐
3. Knowledge and use of guided history taking/anamnesis	Structured history taking by center physicians is essential and a checklist can facilitate this	Checklist for history taking* needs to be present and used as evidenced by interview or urticaria patient file review	☐ ☐
4. Knowledge and use of differential diagnostic algorithm	Center physicians need to be aware of the differential diagnoses of chronic urticaria and know how not to miss them. The guideline algorithm can help with this.	Differential diagnostic algorithm** needs to be present and used as evidenced by interview or urticaria patient file review	☐ ☐

*Part of checklist only is shown

Figure 6 Audit checklist* for GA²LEN Urticaria Center of Reference and Excellence (UCARE) certification.³⁹ EAACI, European Academy for Allergy and Clinical Immunology; EDF, European Dermatology Forum; GA²LEN, Global Allergy and Asthma European Network; WAO, World Allergy Organization. Reproduced from Maurer *et al.* Allergy 2016; Apr 1. doi: 10.1111/all.12901. Copyright © 2016 Wiley, with permission.

Confirming a diagnosis of CSU or CIndU and excluding differential diagnoses remain challenges that require the development of better tools and more awareness. The lack of consistency in diagnosis and outcome tests used between different centres and countries contribute to the difficulties associated with the diagnosis and classification of urticaria.

Throughout a patient's treatment, it is important to consider the whole individual and not just their underlying pathophysiology and symptoms. Despite the availability of international and national guidelines, much heterogeneity still exists in the treatment of urticaria globally. GA²LEN Urticaria Centers of Reference and Excellence (UCAREs) may ultimately help to optimize the patient journey in the management of CU.

[\[Click here to test your knowledge\]](#)

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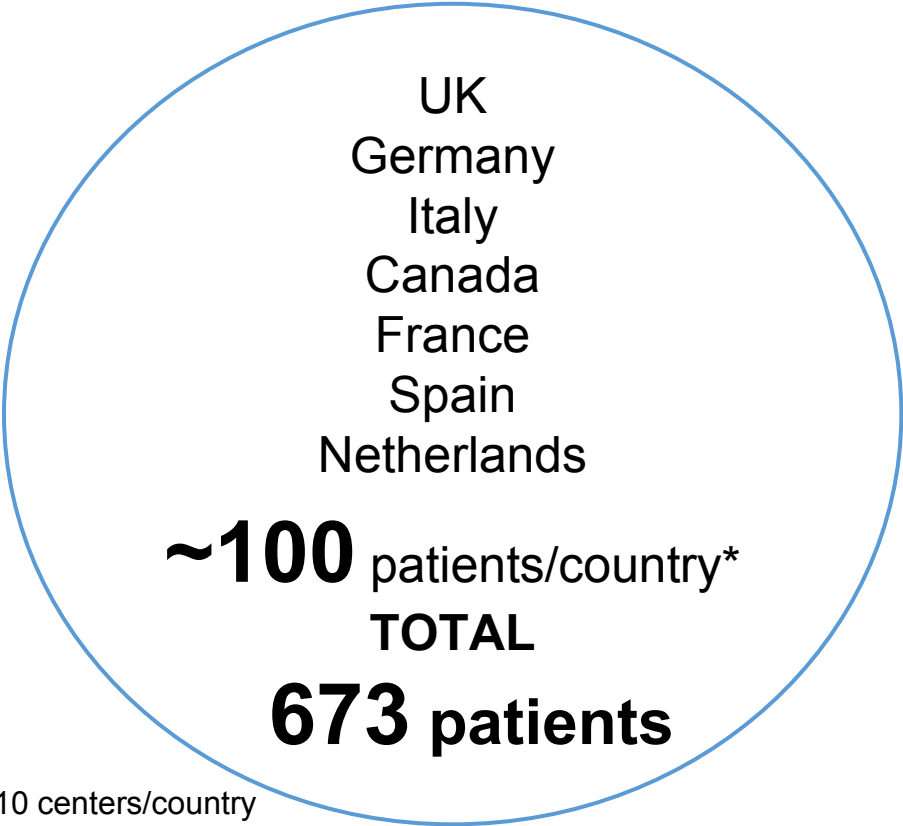
What is ASSURE-CSU?

Identify and quantify the economic and humanistic burden-of-illness in patients with CSU whose disease persists for >12 months and are symptomatic despite treatment

Retrospective medical chart review

Patient demographics
Medical history
Treatment patterns

Total healthcare
resource utilization
and associated costs



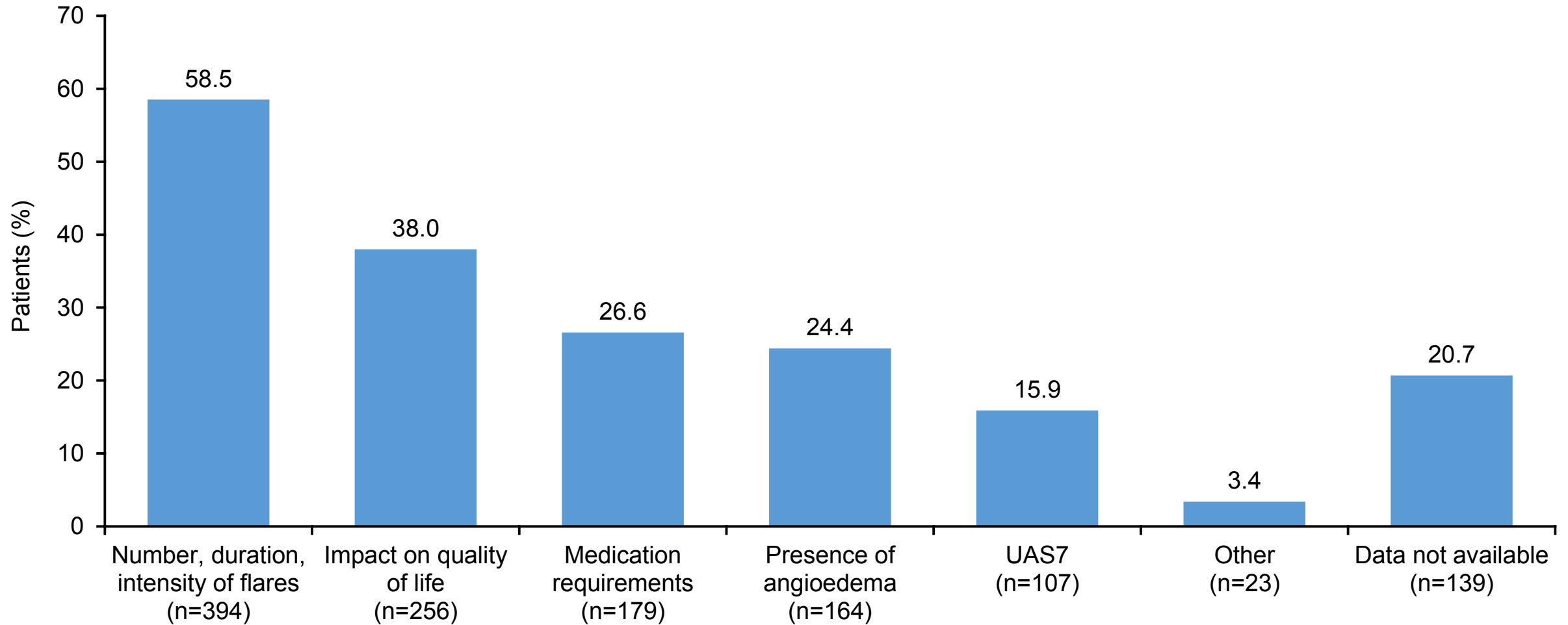
Cross-sectional assessment of PROs and patient diary

CU-Q₂oL, DLQI, EQ-5D
Angioedema description
AE-QoL, UAS7, WPAI

Other medical resources
Out-of-pocket costs

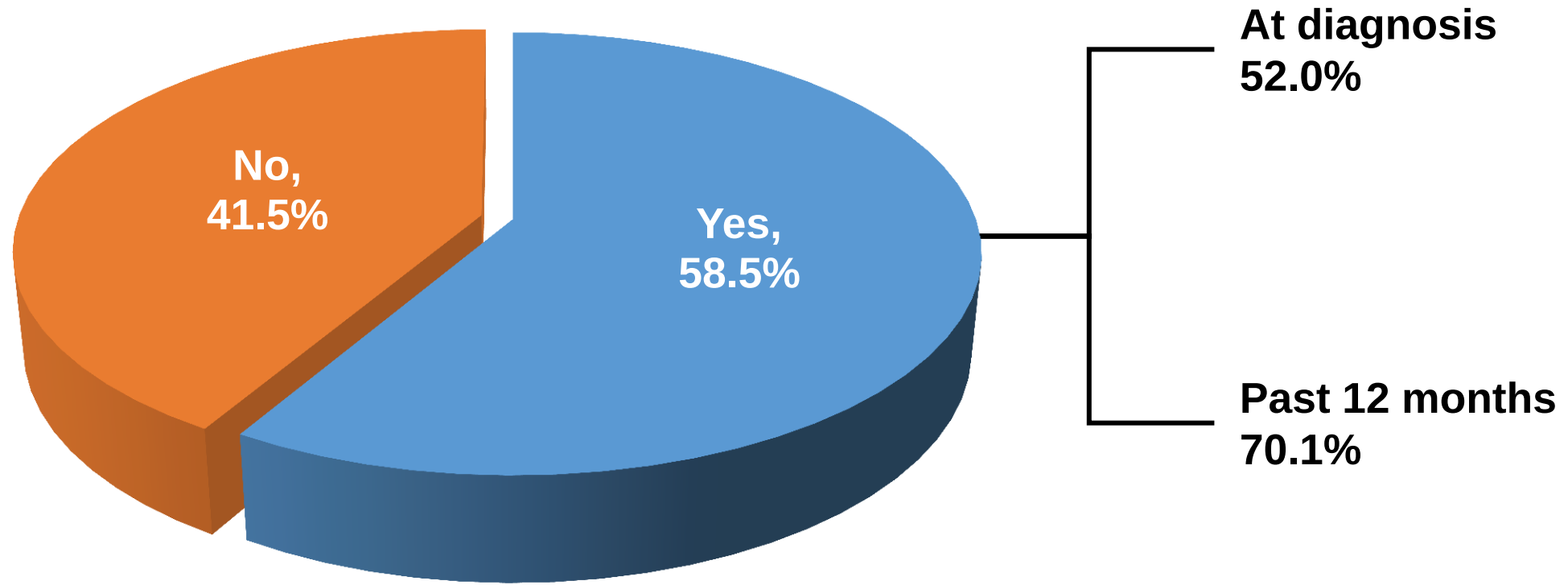
*France - 13 centers and for rest of the countries - up to 10 centers/country
AE-QoL = Angioedema Quality of Life; CSU = chronic spontaneous urticaria;
CU-Q₂oL = Chronic Urticaria Quality of Life Questionnaire; DLQI: Dermatology Life Quality Index;
EQ-5D-3L = EuroQol 5 Dimensions-3 Levels UAS7 = weekly Urticaria Activity Score;
WPAI = Work Productivity and Activity Impairment.

ASSURE-CSU: criteria used by physicians to assess disease severity



UAS7 = weekly Urticaria Activity Score.

ASSURE-CSU: proportion of patients with angioedema associated with CSU



Mean (SD) number of angioedema episodes/patient/year was **19.0** (42.13)

Diagnostic tests

The EAACI/GA²LEN/EDF/WAO Guideline recommends only very limited routine diagnostic measures in Chronic Spontaneous Urticaria

ROUTINE

- CRP/ESR
- Differential Blood Cell Count

EXTENDED

- Infectious diseases
- Type I allergy
- Functional auto antibodies
- Thyroid hormones
- Physical tests
- Pseudo allergen free diet
- ASST

CSU: differential diagnoses

While CSU is the most likely diagnosis in patients with recurrent hives and angioedema, differential diagnoses are possible

HIVES	ANGIOEDEMA
• Acquired autoinflammatory disorders, e.g. • Schnitzler’s syndrome • Systemic-onset juvenile idiopathic arthritis (sJIA) • Adult-onset Still’s disease (AOSD) • Hereditary autoinflammatory disorders, e.g. • Cryopyrin-associated periodic syndromes (CAPS) such as – familial cold auto-inflammatory syndromes (FCAS) – Muckle-Wells syndrome (MWS) – neonatal onset multisystem inflammatory disease (NOMID) – hyper-IgD syndrome (HIDS) – TNF receptor alpha-associated periodic syndrome (TRAPS) • Urticarial vasculitis	• Hereditary angioedema (HAE) • Acquired angioedema due to C1-inhibitor deficiency (AAE) • Angiotensin converting enzyme (ACE) inhibitor-induced angioedema

CSU = chronic spontaneous urticaria; Ig D = immunoglobulin D; TNF = tumor necrosis factor.

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Asking and listening

- I ask around beginnings and exacerbations
- 'Smorgasbord' question
- Encourage some detail
- Frequently, the right 'stuff' will emerge
- I don't get worried by distress

Responding

- Hear
- Understand and empathise
- Educate regarding the connections
- Don't try and 'make it better' – avoid the 'fix-it' attitude
- Don't '*psychiatrize*'
- See what they do with it

Warm 'holding'

- Remain empathic
- Do the medical things well (honoring both the physical and the non-physical)
- Suggest the patient thinks about it
- Get them back soon
- Believe they might do something with the insights of the session

Take-home messages

- Patients can suffer for years without such whole person data ever ascertained
- Story can be as crucial as the biomedical data
- Addressing feelings and meaning can add a powerful dimension to treatment
- There is an opportunity for clinicians to incorporate a whole-person approach into their ordinary consultations with patients
- There is a need for properly structured studies that incorporate whole person and standard drug therapy regimens with standard therapy

GA²LEN Urticaria Centers of Reference and Excellence (UCAREs)

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The burden of chronic spontaneous urticaria

The EAACI/GA²LEN/EDF/WAO urticaria guideline defines chronic spontaneous urticaria (CSU) as the spontaneous appearance of hives, angioedema or both for **6 weeks or more.**¹

Chronic spontaneous urticaria

Hives

- Central swelling surrounded by erythema (redness)¹
- Intense itching¹
- Usually resolves within



Angioedema

- Sudden pronounced swelling¹
- Often painful or burning sensation¹
- Can take up to

24 hours¹

72 hours to resolve¹

CSU-associated angioedema was observed in **58.5%** of patients³

In patients with CSU

At diagnosis, the majority of patients have **moderate to severe** disease³

31%
MODERATE

37%
SEVERE



The majority of patients experience symptoms of CSU for **2 years** before they are diagnosed³

1–13% have angioedema and **no hives**²

29–65% have hives and **no angioedema**²

33–67% have hives and **angioedema**²

Up to 1 in 4

of the total population will experience at least one episode of **any type of urticaria** during their lifetime²



673 patients

The ASSURE-CSU study

examined the burden of disease in **673 CSU patients** whose disease had persisted for **>12 months** and who were symptomatic despite treatment^{3,4}



Patients state

swellings, itch, pain, and feelings of being tired, irritable, weak or a feeling of **loss of control over their lives** are the worst aspects of their disease⁵

>30%

Urticaria

impacts many aspects of patients' daily lives and has a **considerable psychological and social burden**, with many (>30%) suffering from psychiatric comorbidities such as anxiety and depression^{2,6}

Burden of disease

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