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REVIEW

Management of urticaria: not too complicated, not too simple

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Summary

In spite of being an old disease and apparently easy to diagnose, chronic spontaneous urticaria (CSU) is still perceived as an uncontrollable and difficult to manage disease. The perception of the patient is that his/her condition is not well understood and that is suffering from a disorder with hidden causes that doctors are not able to tackle. Sometimes patients go through a number of clinicians until they found some CSU expert who is familiar with the disease. It is surprising that myths and believes with no scientific support still persist. Guidelines are not widely implemented, and recent tools to assess severity are infrequently used. European and American recent guidelines do not agree in several key points related to diagnosis and treatment, which further contributes to confusion. With the aim to clarify some aspects of the CSU picture, a group of allergists and dermatologists from the Spanish Dermatology and Allergy societies developed a Frequent Asked Questions leaflet that could facilitate physicians work in daily practice and contribute to a better knowledge of common clinical scenarios related to patients with CSU.

Introduction

Chronic urticaria, defined as urticaria that persists for longer than 6 weeks, is a frustrating condition for both patients and caregivers due to the persistence of lesions in spite of using available treatment options. Chronic spontaneous urticaria (CSU) can be categorized according to the EAACI classification into two main types: chronic spontaneous urticaria (CSU) and physical or inducible urticaria (Table 1) [1]. CSU is defined by the spontaneous appearance of wheals with or without angioedema that persist for ≥6 weeks [1]. CSU is occasionally associated with other types of chronic urticaria, such as inducible (physical or cholinergic) urticaria [2]. The present article is focused on CSU and covers several aspects regarding its diagnosis and management.

Despite the impact on quality of life [3, 4] and the morbidity associated with CSU [3], relatively little is known about the pathophysiology of this condition. Moreover, with the exception of physical urticaria, in the majority of cases, a cause cannot be established. An autoimmune origin is found in a subpopulation of CSU

Table 1. Classification of urticaria [1]

Chronic spontaneous urticaria	Physical or inducible urticaria
Spontaneous appearance of wheals, angioedema or both lasting ≥6 weeks	• Physical urticaria o Symptomatic dermatographism o Cold urticaria o Delayed pressure urticaria o Solar urticaria o Heat urticaria o Vibratory angioedema • Cholinergic urticaria • Contact urticaria • Aquagenic urticaria

patients as assessed by the ability of the patients' sera to activate normal donor basophils and to induce histamine release [5]. However, this subpopulation is clinically indistinguishable from the nonautoimmune group.

There are several guidelines and reviews [1, 6–9] on the management of urticaria. However, these guidelines do not completely agree on key points, such as which test to order or the adequate treatment approach for the different clinical scenarios. This disagreement is even more obvious in the latest published guidelines [1, 10].

Omalizumab has emerged as a treatment that is able to control CSU symptoms in a significant percentage of non-responder patients to antihistamines at high doses or in combination with other drugs [1, 10–12]. Omalizumab also opens a new avenue of research because this drug works both in autoimmune and in nonautoimmune urticaria [13]. Its mechanism of action is not completely understood. Omalizumab is able to capture IgE, down-regulating IgE receptors and preventing IgE binding to its high- and low-affinity receptors, and seems to desensitize mast cells [14]. This drug was approved for the treatment of CSU in March 2014 by the European Medicines Agency (EMA) [15] and the U.S. Food and Drug Administration (FDA) [16].

There are many unsolved issues in CSU, from the underlying lack of large epidemiology studies [17]. In the present review, practical guidance based on common questions related to the clinical management of patients with CSU is provided. We selected key questions from previously published guidelines and updated them using the most recently available evidence obtained from a careful critique of the literature. We also tried to cover a number of topics that are given less attention in current CSU guidelines, such as prognosis, severity assessment and urticaria duration.

Methods

We constituted a national working group of allergists and dermatologist that have a specialized clinic dedicated to CSU. We met during 2012–2013 every 2 months to discuss the outcomes of each stage of the review and set the next step to take. We first generated a list of issues that emerge when approaching a patient suffering from CSU. From this list, we generated a list of specific questions that address each point. We then distributed the questions, that were distributed previously in the meetings, among the participants and worked remotely on each answer. Frequently asked questions with direct clinical relevance were chosen by the authors. Answers to these questions and summaries of key points were agreed upon by consensus. The questions were numbered and grouped into sections related to diagnosis, clinical evaluation and follow-up, as well as treatment and management in special cases.

A review of the literature on chronic urticaria (from January 1st, 2009, up to December 1st, 2013) was performed by an independent documentalist using the MEDLINE database through a PubMed search. The search strategy included retrieval of documents with the following words included in the 'Title' field: 'urticaria', 'idiopathic', 'chronic', 'diagnosis', 'prognosis', 'assessment', 'duration', 'severity', 'quality of life', 'treatment', 'management' and 'omalizumab'. The search was performed using these terms separately or combined to explore all possibilities. Additionally, publications included in the field 'Related citations in PubMed' appearing together with the Abstract of retrieved citations were reviewed. Other filters included 'review' for the category of article type and 'full text available' and 'free full text available' for the category of text availability. In all cases, the title and abstract of the articles were carefully read, and suitable articles were selected based on the study content. The references of retrieved documents were also checked for articles of interest. A final list of articles with the corresponding abstracts and the full text were distributed to the authors. This information and documents from their own files were used as a scientific background for the review.

Results

Diagnosis of CSU, physical examination and complementary testing in chronic urticaria (work-up studies)

What are the clinical features of CSU? What are the characteristics of the macroscopic and microscopic cutaneous lesions?. Chronic spontaneous urticaria skin lesions are transient and pruritic and appear daily or almost daily for at least 6 weeks. This condition is

accompanied by angioedema in 40–50% of patients [18, 19]. The hives last <24 h, with no skin lesion upon disappearance. However, interstitial oedema with a perivascular infiltrate containing lymphocytes, monocytes and eosinophils is observed in all cases [20]. Neutrophils and basophils may also be observed, and $CD4^+$ T cells [21, 22] are also present. In cases of angioedema, the same histological findings are found, but the interstitial oedema is more intense.

Key point: Chronic urticaria lesions consist of evanescent wheals or hives surrounded by erythema.

What exacerbating factors are known?. The large majority of patients have no evidence of any exacerbating factor. The only recognized trigger for CSU is nonsteroidal anti-inflammatory drugs (NSAIDs) [23, 24]. In patients presenting with CSU associated with a degree of physical urticaria (Table 1) [1], symptoms may be exacerbated when in contact with the corresponding stimulus, such as pressure in the case of delayed pressure urticarial, or scratches in the case of dermatographic urticaria.

Key point: NSAIDs are the main factor that exacerbates CSU.

What is the natural clinical course?. The natural course is unpredictable. CSU undergoes spontaneous remission, with relapses in most cases. Few epidemiological studies have explored the duration of symptoms. Gaig et al. [2] found that in 70% of cases, chronic urticaria lasted one year, whereas in 11% of patients, it lasted for more than 5 years. In a prospective study of 139 patients followed over 5 years, the duration of urticaria correlated with its severity of urticaria, the presence of angioedema and positive autoimmune markers (positive autologous serum skin test [ASST] and antithyroid antibodies) [19]. That study found that 70% of patients had hives that lasted more than one year and 14% had symptoms 5 years after the end of the study period, durations very similar to those reported in other studies [2, 25].

Key point: The evolution of CSU is unpredictable, with spontaneous remissions and relapses. No prospective and retrospective neither studies have examined the influence of treatments on the natural course of CSU.

Is it necessary to perform extensive diagnostic studies by complementary testing in all patients with CSU?. The indiscriminate search for underlying causes that may include an extensive battery of tests is discouraged [1, 6–9] due to low cost-effectiveness. A careful and detailed medical history and physical examination are essential. Patient-oriented questions are helpful to establish the type of chronic urticaria and to define baseline laboratory studies and/or other complementary tests tailored to the individual patient (Table 2). In most cases, there is no need to order an extensive work-up unless data from the clinical history suggest an underlying disease. Table 3 lists the essential tests that should be performed.

Key point: Unless suggested by the clinical history, there is no need to perform extensive tests when examining a CSU patient.

Table 2. Recommended data to obtain from the patient's medical history

Duration of symptoms
Family history of urticaria
Duration of wheals, if residual skin lesions
Intensity and characteristics of pruritus
Associated subjective symptoms (e.g. pain, burning sensation)
Diurnal variation of signs and symptoms
Appearance of urticaria in relation to weekends, holidays and trips (abroad)
Size, shape and distribution of hives
Frequency and localization of associated angioedema
Concomitant systemic symptoms (e.g. joint pain, headache, nausea, vomiting, fever)
Family history of urticaria or atopy
Seasonal variation of symptoms
Appearance of signs and symptoms in association with physical stimuli (e.g. cold, heat, friction)
Psychiatric or psychosomatic disorders
Use of drugs (e.g. Nonsteroidal anti-inflammatories, hormonal treatments, topical agents, alternative remedies) and its relationship with urticaria
Relationship with the menstrual cycle
Use of substances/tobacco, and particularly the use of flavoured cigarettes or cannabis
Occupation and hobbies
Quality of life related to urticaria and emotional impact
Previous treatments and responses
Previous diagnostic studies and results

Table 3. Minimal work-up studies on chronic spontaneous urticaria*

Clinical history (see Table 2)
Physical examination
Urticaria activity score (UAS) and angioedema activity score (AAS) at the time of physical examination
Assessment of quality of life (CU-Q2oL)
Performance of appropriate tests to rule out physical urticaria
Blood count, thyroid antibody and thyroid function tests and assessment of the sedimentation rate and serum C-reactive protein
Skin prick test to rule out allergy when patient's history suggests that an allergic disease may be involved.
Skin biopsy, if indicated

*As an optional work-up study ASST (Autologous serum skin test) and an assessment of the *in vitro* ability of sera to stimulate normal basophils (CD63 or histamine release test) could be performed.

Table 4. Differential diagnosis of chronic urticaria

Diseases or syndromes with typical urticarial lesions	Autoinflammatory diseases
	Schnitzler syndrome
Diseases with fixed urticarial lesions with atypical features	Cutaneous lupus erythematosus
	Fixed drug eruptions
	Bullous pemphigoid
	Reticular erythematous mucinosis
	Erythema multiform

What is the differential diagnosis to be established for a patient with CSU?. Apart from urticaria vasculitis for which diagnosis is made through biopsy, It can be difficult to differentiate hives from other dermatoses [26] (Table 4). However, the natural course differs in these pathologies. Erythema multiform clears on its own within a maximum of 3 weeks; it is included in the differential diagnosis because of its severity and should always be ruled out at the onset of symptoms, when it can resemble chronic urticaria. Autoinflammatory syndromes [27] have symptoms that may be confused with chronic urticaria, but they are rare, and although skin rashes are always associated with systemic symptoms, itching is not as striking a feature as it is in the case of chronic urticaria. Certain systemic diseases are associated with urticaria-like lesions, such as systemic lupus erythematosus, Schnitzler syndrome (IgM monoclonal gammopathy, urticaria, fever, lymphadenopathy and weight loss), mastocytosis and hypereosinophilic syndromes.

Key point: Chronic urticaria differs from other dermatosis on its duration, the evanescence of lesions and intense itching.

Is skin biopsy a mandatory diagnostic tool for the diagnosis of CSU?. Skin biopsy is not mandatory to diagnose chronic spontaneous urticaria, but it is strongly advisable when hives last more than 24 h, to exclude urticarial vasculitis. Certain patients with urticarial vasculitis may exhibit symptoms similar to those of patients with chronic urticaria, with wheals lasting <24 h and with no residual skin lesions [28]. In cases with an unusual presentation of chronic urticaria – that is, mild itching, painful skin lesions or unresponsiveness to antihistamines – or when the diagnosis is not clear, we recommend performing a skin biopsy to rule out urticarial vasculitis.

Key point: Skin biopsy is only recommended when skin lesions last longer than 24 h.

Is it necessary to assess patients for infections or active infestations in the diagnosis of CSU?. Despite being included in several guidelines, no large randomized double-blind, placebo-controlled studies have demonstrated a causative role for infections in CSU. With the exception of certain geographical regions in which specific parasites are endemic [1, 6–9], there is no need to perform a search or treatment for underlying infections.

Key point: The evidence for the role of infection in CSU is very weak. There is no need for a systematic assessment of infection in CSU.

Is food allergy associated with CSU?. Chronic urticaria is not a manifestation of IgE-mediated food allergy. However, in isolated cases, certain true food allergies can mimic chronic urticaria. This has been recorded in allergies to foods containing omega-5 gliadin, lipid transfer protein (LPT) or galactose-alpha-1,3-galactose. On the other hand, it should be noted that in some cases food allergy might occur independently from CSU.

Key point: CSU is not related to IgE-mediated food allergy.

Are food preservatives and additives related to CSU?. - Food additives (such as preservatives and colour additives) and ingredients naturally present in food (such as histamine and aromatic components) have been described as causative or aggravating factors by several uncontrolled studies [1, 7, 29, 30]. However, a recent study yielded only two positive results from a single-blind challenge with 11 food additives of each of 100 patients with chronic urticaria. Moreover, when a double-blind test and a placebo challenge test were performed on these two positive patients, neither reacted to the culprit additive [31]. Avoidance of food preservatives and additives is not therefore recommended.

Key point: There is no need to recommend a restrictive diet to patients suffering from CSU.

Is an assessment of autoimmunity useful from a diagnostic perspective in patients with CSU?. Autoimmunity has long been discussed as a cause of CSU. Although not widely used, assessing serum autoreactivity is useful, this is currently the only office procedure that can help reveal whether an autoimmune mechanism is responsible. The common cluster of autoimmune diseases in patients suffering from chronic spontaneous urticaria, the presence of antithyroid antibodies, and the serum ability to activate normal basophils, supports the etiopathogenic role of autoimmunity. Screening can be performed with the autologous serum skin test (ASST). The correct approach to the ASST is described in an EAACI/GA^{2}LEN position paper [32]. The ASST is a non-specific screening test that evaluates the presence of serum histamine-releasing factors of any type – not just

autoantibodies. According to the experience of many urticaria experts, healthy controls and patients without CSU do not yield a positive ASST [33–41]. Nevertheless, the specificity of this test is still a matter of discussion. The role of coagulation factors in the development of the wheal has been examined using the autologous plasma skin test (APST), but there is still no consensus about that test's use as a diagnostic tool [40, 41]. The only way to screen for functional autoantibodies against either IgE or FcεRI (the high-affinity IgE receptor) is to demonstrate the ability of sera to activate normal basophils, showing either histamine release [42–44] or serum-induced basophil CD63 and/or CD203c expression [45, 46] by flow cytometry. Identifying serum-induced basophil CD63 and/or CD203c expression is the recommended approach [9].

Key point: Autoimmunity could be assessed either through the ASST or by demonstrating *in vitro* the ability to activate normal basophils for diagnosis and prognosis. Patients with a positive ASST result show more severe and longer-lasting disease.

Are there biomarkers of activity in CSU?. The severity of CSU should be evaluated based on the intensity of its clinical symptoms. Several biomarkers, such as interleukin (IL)-6, C-reactive protein and D-dimers, metalloproteinase-9 and complement C3 and C4, have shown distinctive patterns in CSU patients, but these molecules have still not been validated as useful biomarkers.

Key point: Although several substances may show specific levels in CSU patients, they have not yet been validated as CSU biomarkers.

Does isolated angioedema have clinical, therapeutic and/or prognostic implications?. Isolated angioedema with no hives that responds to antihistamines should be explored and phenotyped. Most guidelines [1, 6–8] include isolated angioedema as a subtype of CSU. However, this condition does not share the typical features of chronic urticaria, such as being more frequent in women or having an autoimmune profile. In certain cases, typical CSU starts with isolated angioedema that evolves into cutaneous wheals. On the other hand, histaminergic angioedema is clearly different from bradykinin-mediated angioedema [47], which does not respond to antihistamines or corticosteroids, has a different physiopathology [48–50] and requires a different treatment approach [51, 52]. The differential diagnosis for isolated angioedema is shown in Table 5 [53].

Key point: Isolated angioedema does not share the typical features of CSU.

How should the diagnosis of CSU in children be approached?. Chronic spontaneous urticaria is less frequent in children, but in general, it shares the underlying causes and physiopathology of CSU in adults. Therefore, the diagnostic approach in children and adults is the same [26, 54, 55]. However, it should be noted that infants are more prone to develop acute urticaria secondary to an infection.

Key point: The diagnostic approach to CSU in children should be the same as that in adults.

Table 5. Differential diagnosis of isolated angioedema

Type	Normal C1-INH	Decreased C1-INH	Abnormal C1-INH
Acquired	Idiopathic histaminergic angioedema Bradykinin-induced angioedema Angioedema due to ACE inhibitors	Acquired angioedema with C1-INH deficiency	
Hereditary	Hereditary Angioedema of unknown origin Hereditary Angioedema with FXII mutations	Type I hereditary angioedema	Type II hereditary angioedema
Other	Delayed pressure angioedema Angioedema due to NSAID intolerance		

Modified from Cicardi et al. [53].

Clinical evaluation and follow-up

How can the activity of CSU be measured?. The EAACI/GA^{2}LEN/EDF/WAO consensus [1] recommends the use of a single language in the form of well-established and simple scales, such as the urticaria activity score (UAS) [56] and the related scale, UAS7[57] (Table 6). The number of wheals and the intensity of pruritus are scored individually for the past 24 h using a 3-point Likert scale from 0 (no disease activity) to 3 (intense activity). The sum of the scores represents disease severity on a scale from 0 (minimum) to 6 (maximum). The UAS7 is calculated as the sum of the intensity of pruritus and the number of wheals over 1 week (minimum score 0, maximum score 42). UAS and UAS7 are also recommended in other guidelines [1, 8]. These tools have been used in controlled clinical trials and have recently been validated for use in the follow-up and monitoring of disease activity in patients with CSU [58, 59] Additionally, the British Academy of Dermatology guidelines [9] recommend the use of a diary card to

Table 6. Urticaria activity score

How many wheals have appeared during the last 24 h?	Scoring
None	0
Mild (<20 wheals/24 h)	1
Moderate (20–50 wheals/24 h)	2
Intense (>50 wheals/24 h)	3
How severe was the itching during the last 24 h?	
None	0
Mild (present but not annoying or troublesome)	1
Moderate (troublesome but does not interfere with normal daily activity or sleep)	2
Intense (severe itch that is sufficiently troublesome to interfere with normal daily activity or sleep)	3

record the frequency, duration and severity of urticarial episodes. Another tool is the visual analogue scale (VAS) (100-mm line) is a commonly used tool for self-reporting pruritus intensity and for assessing the level of sedation by antihistamine treatment [60–62].

Key point: The UAS and UAS7 should be used to assess the severity of CSU and the treatment response.

Are there any indicators of severity or poor prognosis in CSU?. A systematic review of 34 studies that evaluated parameters relating to the severity measured through different scoring symptoms and duration of chronic urticaria suggested that disease severity may predict the duration of the disease [63]. Other CSU features related to severity and duration are angioedema, association with physical urticarias, old age and positive antithyroid antibodies [64–67]. Similarly, a positive ASST has been shown to be associated with more severe symptoms [68, 69]. In the most recent retrospective study, which included 223 patients with CSU, the only prognostic factor was age, with no correlation found between severity or duration and angioedema [25]. Regarding biomarkers, the plasma levels of prothrombin fragments 1 + 2, D-dimers and C-reactive protein may function as markers of CSU severity [63], but threshold values with predictive capacity have not yet been defined.

Key point: The duration of the disease is longer in patients with more severe disease, angioedema, a positive ASST result, physical urticaria and old age.

Are health-related quality-of-life questionnaires useful in the assessment of CSU?. Health-related quality of life is increasingly recognized as an essential parameter for assessing the condition of chronic urticaria patients [59] and as an outcome measure in clinical trials. The need to measure the impact of chronic urticaria on the patient's quality of life is consistently encouraged in the different clinical guidelines, but specific recommendations for use are not included. To date, the only questionnaire specifically developed to measure health-related quality of life in chronic urticaria patients is the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) [70, 71]. Other nonspecific quality-of-life instruments used in studies of chronic urticaria include the Dermatology Life Quality Index (DLQI, which has been shown to be a valid, reliable and clinically useful outcome measure for assessing quality of life in chronic urticaria [72], the Nottingham Health Profile (NHP) [73], the World Health Organization Quality of Life Assessment-Brief (WHOQOL-BREF) [74] and Skindex-29 [75, 76]. When compared to healthy controls, patients with chronic urticaria had significantly higher scores in the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI) [73]. Additionally, the interference of CSU with sleep may account for a reduction of up to 30% in work/school productivity, as assessed using the Work Productivity and Activity Impairment instrument [77].

Key point: The CU-Q2oL is the only available instrument specifically developed to assess the quality of life of chronic spontaneous urticaria patients.

Can response/nonresponse to the drugs used in the treatment of chronic spontaneous urticaria be predicted?. Autoimmunity and CSU associated with physical urticarias are more resistant to treatments [68]. Patients with predominant neutrophil tissue infiltration are believed to be less responsive to antihistamines. A recent study suggests that elevated D-dimer levels are able to predict the response to antihistamines treatment [78, 79].

Key point: No predictors of treatment response are available for CSU.

Treatment of CSU

Antihistamines. What range of doses is more appropriate for antihistamines?: Nonsedating H_1-antihistamines at licensed doses are the recommended first-line treatment in mild-to-moderate chronic urticaria [1]. In patients with severe, recalcitrant urticaria in whom the standard dose is not effective, there is evidence that increasing the dose up to fourfold might control symptoms, without compromising the patient's safety [80, 81]. There have been no well-designed, randomized double-blind clinical trials comparing the efficacy of therapeutic and upgraded doses. Some studies have been performed in spontaneous chronic urticaria and in certain forms of inducible chronic urticaria [82] using desloratadine (up to 20 mg), levocetirizine (up to 20 mg), cetirizine (up to 30 mg), fexofenadine (up to 240 mg), rupatadine (up to 20 mg) and bilastine (up to 80 mg) [83], but they have had mixed results. Limited data are available for updosing, but considering the good safety profile of most second-generation antihistamines, it might be worth evaluating

the efficacy of antihistamines at higher-than-licensed doses before switching to other therapies [80, 81]. Regarding the best way to apply this treatment, the guidelines advise to employ high doses of antihistamines as a second treatment step. However, as in the case of cold urticaria, a useful approach may include starting with four times higher dose, with subsequent dose reduction in the presence of a clinical response.

Key point: Given the safety of most antihistamines, doses can be increased up to four times the standard dose on an individual basis.

Can switching from one antihistamine to another attain an individualized response?: According to the British [9] American [10] and EAACI 2014 [1] guidelines, all patients should be offered a choice between two or more nonsedating H_1-antihistamines, because individual differences in response and tolerance to different antihistamines have been reported.

Is it useful to combine different antihistamines (i.e. sedating and nonsedating)?: In patients with severe, recalcitrant urticaria for whom the standard dose is not effective, combinations of antihistamines are frequently used as another way of updosing. This might involve, for example, two different second-generation antihistamines, or a second-generation antihistamine in the morning and a first-generation antihistamine in the evening. However, first-generation antihistamines are no longer recommended in chronic urticaria [84], and the clinical benefit of combining antihistamines is probably limited when H_1-receptors are already occupied by another H_1-antihistamine.

Key point: There are no studies that demonstrate that treatment with the combined use of sedating and nonsedating antihistamines is more effective than updosing the same antihistamine.

Is it useful to combine H_1- and H_2-antihistamines?: Several relatively small studies have shown that combined use of H_1-antihistamines and H_2-antihistamines (cimetidine, ranitidine) may be more effective than using H_1-antihistamines alone [85, 86]. This effect is related to an increase in the plasma levels of H_1-antihistamine [87], most likely due to a pharmacologic interaction with the isoenzyme cytochrome P-450 in the liver. This phenomenon does not occur when cimetidine is associated with cetirizine [88]. Accordingly, a review of recent studies does not allow confident decision-making about the use of H_2-receptor antagonists in urticaria [89].

Regarding the use of anti H2 antihistamines, most guidelines deleted this point but the American guidelines [10].

Should treatment for CSU be provided on-demand or in a sustained manner?: The beneficial effects of nonsedating H_1-antihistamines given on demand appear to be low [90].

Key point: Nonsedating H_1-antihistamines should be given in a sustained manner.

Does antihistamines induced somnolence affect its use of in CSU?: It is well known that H_1-antihistamines cause sedation, somnolence and fatigue, leading to impairment of cognitive function, memory and psychomotor performance. A position paper of the Global Allergy and Asthma European Network (GA^2LEN) [84] highlights the risk posed by the fact that first-generation H_1-antihistamines, all of which are sedating, are generally regarded as safe simply because of their long-standing use. Given the unwanted side-effects and potential dangers of first-generation H_1-antihistamines, newer, nonsedating second-generation H_1-antihistamines with superior risk/benefit ratios (which are widely available at competitive prices) are strongly recommended.

Key point: Nonsedating antihistamines are recommended for CSU treatment.

Nonantihistamine medications. Should corticosteroids be used in the treatment of CSU?: Controlled clinical trials have not provided any evidence supporting long-term treatment with systemic steroids in CSU, and the prolonged use of steroids is not recommended due to their side-effects. Short courses of systemic steroids could be used in patients with severe exacerbation episodes [91], particularly when accompanied by angioedema or in patients with a minimal or partial response to antihistamine treatment [6, 8]. The dosages and weaning regimens of steroids for urticaria are variable, ranging from progressive reduction over 10 days to complex therapeutic regimens with alternate-day dose reduction.

Key point: Corticosteroids are not recommended as long-term CSU therapy. However, a short course of steroids might be useful to control exacerbation.

In which patients with CSU may oral calcineurin inhibitors be used as an therapeutic option in CSU?: Four randomized controlled trials have reported favourable effects from the use of cyclosporine in patients with chronic urticaria/angioedema who are unresponsive to high doses of second-generation antihistamines [8]. Treatment for 2–4 months has been used, with better results [92]. One study [93] noted improvement after discontinuation of cyclosporine, one-third of patients had complete remission, one-third had their disease controlled with antihistamines, and one-third returned to the severity level previous to cyclosporine therapy. However, cyclosporine has serious side-effects that may outweigh its benefits – especially the high risk of developing renal injury. Minimal data are available on the use of tacrolimus in chronic urticaria [94]. However, the place of cyclosporine has varied as the approval of omalizumab as an indication for CSU.

Key point: Cyclosporine may be considered as an off-label therapeutic option for controlling CSU in patients who are refractory to antihistamines and omalizumab.

What is the role of oral antileukotrienes in the treatment of CSU?: The efficacy of antileukotrienes has been reported in small randomized double-blind studies [95–97] with inconsistent results. Monotherapy with antileukotrienes is not advisable [98].

Key point: The evidence supporting leukotriene inhibitors as a therapeutic option in CSU is weak, and their use in CSU is not recommended.

Which patients with CSU should be treated with omalizumab?: The efficacy and safety of omalizumab have been demonstrated in two randomized, placebo-controlled phase III studies in patients with CSU who remained symptomatic despite H_1-antihistamine therapy at the approved dose [11, 99]. A third study [12] primarily evaluated the safety of omalizumab in patients with CSU who remained symptomatic despite treatment with H_1-antihistamines at up to four times the approved dose, and with H_2-antihistamine and/or leukotriene inhibitors treatment. Omalizumab is the only drug indicated in Europe and the United States as an add-on therapy for the treatment of CSU in adult and adolescent (12 years and older) patients with an inadequate response to H_1-antihistamine treatment [1, 6, 8].

Key point: Consideration should be given to the thesis that patients suffering from CSU with no response to treatment at high doses of H_1-antihistamines should be treated with omalizumab [100].

What is dosage of omalizumab is recommended for refractory CSU?: Omalizumab dosage in CSU has been evaluated in three phase III clinical trials that assessed clinical endpoints such as pruritus control, the number of wheals, the UAS and UAS7 and episodes of angioedema. The recommended dose of omalizumab is 300 mg administered subcutaneously every 4 weeks, as this amount ensures maximum efficacy without serious safety concerns. Although other doses achieved statistical significance for the primary endpoints and most of the secondary endpoints, it was concluded that 300 mg provided the best benefit–risk profile for most adult patients, regardless of other variables, such as body mass index and IgE levels. Other retrospective, noncontrolled, observational studies also reported significant symptom control with different doses and scheme protocols [101, 102]. However, large randomized double-blind, placebo-controlled clinical trials should be performed before these protocols could be recommended.

Key point: Omalizumab is recommended for use in refractory CSU at 300 mg administered subcutaneously every 4 weeks.

What side-effects are associated with omalizumab treatment in CSU?: In randomized trials, side-effects reported in more that 3% of patients receiving consisted in headache, diarrhoea, joint pain, dysmenorrhoea and upper respiratory tract infections, without differences between the groups receiving active treatment and placebo [103].

Key point: Omalizumab given at 300 mg has a favourable safety profile.

When can treatment with omalizumab be discontinued or modified?: In a phase III study, Kaplan et al.[104] reported that after discontinuation of omalizumab, most patients recurred in a 10-week period. Interestingly, an acute rebound of hives was not observed, and reappearance of symptoms was slow. It has also been reported that retreatment is effective [105]. In another study in which omalizumab was reintroduced in 20 (47.5%) patients because of recurrence of symptoms, control was achieved in 18 patients (90%), indicating a good retreatment rate with omalizumab [101].

Key point: Once discontinued, retreatment with omalizumab has a good response rate. No rebound effect upon withdrawal of omalizumab has been observed. After 6 months of therapy, most patients return to their baseline level [11, 12] so further studies regarding duration of treatment are needed.

Third-line therapies: The use of other therapies for CSU is based in clinical trials with low evidence level (doxepin, nifedipine, warfarin or hydroxychloroquine), uncontrolled and/or case series studies (methotrexate, mycophenolate, interferon, intravenous gammaglobulin, colchicine, thyroid hormone treatment, phototherapy). One recent double-blind, placebo study of dapsone suggests efficacy [106] but the placebo group has very low response rate so the efficacy may be inflated. Sulfasalazine is better studied [107] than most of the other agents listed but without clear control groups. Both tranexamic acid and cromoglycate showed no efficacy in placebo-controlled trials. Two recent reviews cover extensively available options and studies published in the literature on third-line and fourth-line therapies in CSU [108, 109].

Management in special cases

How should CSU be managed in children?. Several studies have assessed the efficacy of treatment in paediatric patients with chronic urticaria, and recommendations for adults have been extrapolated to children [7, 9, 110]. The treatment of choice is standard dosage of second-generation H_1-antihistamines, according to the products' technical specifications. Currently, ketotifen and cetirizine can be used in infants from the age of 6 months; levocetirizine, loratadine, desloratadine and ebastine can be used from 2 years of age; and rupatadine can be used from 6 years of age. Recent guidelines [1, 8] include specific recommendations to avoid first-generation H_1-antihistamines due to the probable

impact on school performance. There are reports of successful use of cyclosporine in children [111, 112] similar to the response found in adults. There is little evidence of the efficacy of other therapeutic alternatives, such as systemic corticosteroids, dapsone, omalizumab, intravenous immunoglobulins and plasmapheresis; these options should be evaluated on an individual basis in cases of severe refractory chronic urticaria [1, 7, 9, 113, 114]. None of the currently licensed antihistamines is contraindicated in children aged 12 or older, according to the British Association of Dermatologists Therapy Guidelines and Audit Subcommittee [9]. As dosing and age restrictions for individual products vary in younger children, it is recommended that the relevant datasheets be consulted before prescribing antihistamines in children.

Key point: CSU in children should be managed in the same way as for adults.

A suggested treatment approach is included in Figure 1. It should be noted that as omalizumab is just approved as an add-on therapy, long-term data are needed to assess that omalizumab is safer and better cost-saving alternative than the remaining therapies available.

How should CSU be managed during pregnancy and lactation?. During pregnancy, urticaria should be controlled using the minimum level of medication that is effective [115]. The use of H_1-antihistamines (preferably second-generation) should be considered as the first therapeutic step. However, no H_1-antihistamine agent is in category A regarding safety in pregnancy. Category B of safety in pregnancy has been assigned to loratadine, cetirizine, levocetirizine and chlorpheniramine. Hydroxyzine is the only antihistaminic drug that is contraindicated in pregnancy, as specifically mentioned in the product's specifications.

Lactation could also pose a challenge to treat CSU. During lactation, loratadine and cetirizine are the only H_1-antihistamines recommended for use. The minimum possible dose of H_1-antihistamines and the shortest duration of treatment should be used, but only when the benefits outweigh the potential risks. H_1-antihistamine is excreted in breast milk. Chlorpheniramine can cause sedation and poor feeding in babies so should be avoided [7].

As it is the case in rheumatologic diseases [116, 117] or asthma [118], in CSU [109] systemic corticosteroids may be administered in pregnancy but only at the lowest possible doses and for the minimum period of time due to potential areas of concern, including congenital malformations during the first trimester of pregnancy, neonatal adrenal insufficiency and low birthweight. However, the absolute risk is low. Moreover, systemic corticosteroids have the potential risk of inducing hypertension, gestational diabetes and preterm delivery due to the premature rupture of membranes. Corticosteroids appear to be safe for nursing infants because of low levels in breast milk. The concentrations in breast milk are generally 5–25% of maternal serum levels, with rapid and bi-directional exchange between the serum and breast milk. When high doses are required, it is reasonable to delay breastfeeding for up to 4 h after each dose of steroids. Prolonged treatments and high doses of systemic corticosteroids should be avoided.

Key point: During pregnancy and lactation antihistamines, labelled as B category should be used as first-line therapy in urticaria, using the minimum level of medication that is effective.

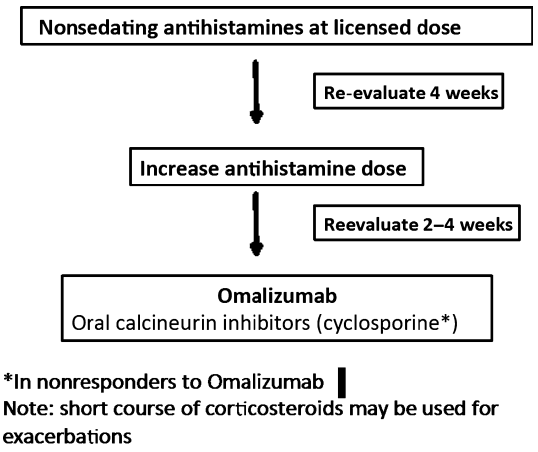

Fig. 1. CSU treatment algorithm (CSU management with treatment options supported by strong evidence). Use of omalizumab as a first-line treatment once patients are shown to be refractory to antihistamines (in agreement with the most recent review) [100].

Concluding remarks

Due to the lack of knowledge of the physiopathological CSU mechanisms, a plethora of causative theories and alternative therapies have always emerged. CSU landscape has greatly changed. We now have much better tools to assess severity and quality of life. More importantly at the present time, we could offer a real hope to control symptoms to these desperate patients. For that reason, it is very important to provide physicians with updated knowledge. Delivering clear and simple recommendations on when and how apply these new tools and treatments also reinforces good clinical practice that in turn will greatly improve patients' life and healthcare performance. It is quite discouraging to observe differences between the American and European CSU diagnosis and treatment approaches. Both sides have points to make and each of them has strengths and weaknesses. We tried to offer a FAQ (Fre-

quent Asked Questions) section for the physician who approaches a CSU patient. Our main point would be to take into consideration the recent existence of a very effective treatment and not to continue offering outdated treatment options.

Conflict of interest

Dr. Ferrer is on the scientific advisory board and a speaker for Novartis, and FAES, has served on the scientific advisory board for Genentech, receives research grant from Novartis and has received speaker honorarium from MSD, Novartis, FAES and GSK. Dr Bartra reports have served as consultant to Novartis, Faes Farma, Hal Allergy, had been paid lecture fees by Novartis, Stallergenes, UCB, Thermofisher, Menarini and Chiesi. Dr. Gimenez-Arnau is on the scientific advisory board of Uriach Pharma, Genentech and Novartis, has received research grants supported by Uriach Pharma, Pharma and Novartis and is a speaker for Uriach Pharma, Novartis, Genentech, Menarini, GSK and MSD. Dr. Jauregui has acted as a paid consultant or medical writer for Novartis, FAES farma and Pfizer and has also received speaker honorarium from MSD and FAES farma. Dr. Labrador-Hornillo has acted as a paid consultant for Novartis and Shire having received speaking honorarium from Novarits and Shire having also received research grant from Thermophisher. Dr. Ortiz de Frutos has acted as a paid consultant for Novartis and has received research grants from Astellas and Leo Pharmaceuticals. Dr. Silvestre has acted as a paid consultant for Novartis. Dr. Sastre reports have served as consultant to Thermofisher, MSD, Sanofi, Novartis, Faes Farma, Gennetech, Roche and GSK, have been paid lecture fees by Novartis, GSK, Stallergenes, UCB, Thermofisher; as well as having received grant support from Thermofisher, GSK and ALK-Abello. Dr. Velasco acted as a paid consultant for Novartis. Dr. Valero reports have served as consultant to Faes Farma, Chiesi, Orion Pharma, MSD, Novartis, UCB, Uriach Pharma, GSK, Stallergenes, have been paid lecture fees by Novartis, GSK, Stallergenes, Chiesi, Leti, Thermofisher; as well as having received grant support from Novartis, Faes Farma, Uriach Pharma.

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