Chronic spontaneous urticaria guidelines: What is new?

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Urticaria is a heterogeneous inflammatory disorder that can be acute or chronic and is defined by the appearance of wheals, angioedema, or both. Very recently, the newest update and revision of the international European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/Asia Pacific Association of Allergy Asthma Clinical Immunology guideline for the definition, classification, diagnosis, and management of urticaria was published. It aims to help primary care physicians and specialists in the management of their patients with urticaria. The guideline applied the Grading of Recommendations Assessment Development and Evaluations approach to developing consensus recommendations. These recommendations were then discussed in a Delphi conference that included more than 250 specialists in the field, and they are endorsed by more than 50 international societies. Here, we highlight changes from previous versions of the international urticaria guideline and their impact on clinical practice. (J Allergy Clin Immunol 2022;150:1249-55.)

Key words: *Urticaria, angioedema, consensus, guidelines, evidence-based, hives, itch, mast cell, urticaria, wheal*

In the year 2000, the first version of the international urticaria guideline was developed as a European guideline and has since evolved to become a global guideline. This was achieved through updates and revisions every 4 years.[1-5] The development of this guideline as well as its revisions and updates have been driven by the aim of establishing a worldwide consensus on the classification, diagnosis, and treatment of urticaria. In December 2020, the sixth guideline consensus conference was held and the most recent update and revision of the international urticaria guideline was finalized. All international societies were invited to participate. Altogether, 50 national and international societies participated in the most recent update and revision. The American societies involved included the American Academy of Allergy, Asthma & Immunology, the American Academy of Dermatology, the American College of Allergy, Asthma and Immunology, the Brazilian Association of Allergy and Immunopathology, the Mexican College of Clinical Immunology and Allergy, the Canadian Society of Allergy and Clinical Immunology, the Latin American Society of Allergy and Immunology, the Paraguayan Society of Immunology, Asthma and Allergy, and the World Allergy Association. The most recent updated and revised international urticaria guideline was published in 2021.[5]

Like previous updates and revisions of the guideline, the current version used the Grading of Recommendations Assessment Development and Evaluations (GRADE) approach, which is considered the most rigorous and comprehensive methodology for the development of scientific evidence–based guidelines.[3] A global expert panel consisting of delegates of each involved society drafted recommendations to be included in the updated and revised guideline. These recommendations were reviewed and voted on during the Delphi consensus conference held in Berlin, Germany. Because of the COVID-19 pandemic, this conference was organized as a hybrid event, allowing urticaria specialists from all over the world to participate. As a result, 24 recommendations were included in the current guideline version, which was endorsed by all societies involved.

Although the current international urticaria guideline shares some recommendations with previous versions, there are several key differences, which we highlight and discuss in this review.

METHODOLOGY

The current international urticaria guideline brings on board the Appraisal of Guidelines Research and Evaluation instrument and the methods suggested by the GRADE working group. The literature review was conducted using the

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Abbreviations used

AECT: Angioedema Control Test
CSU: Chronic spontaneous urticaria
EtD: Evidence-to-decision
GRADE: Grading of Recommendations Assessment Development and Evaluations
PROMs: Patient-reported outcome measures
QoL: Quality of life
TPO: Thyroid peroxidase
UCT: Urticaria Control Test

methods provided by the Cochrane Handbook for Systematic Reviews of Interventions.[3,5,6]

Experts from 50 societies were nominated to be involved in development of the guideline's update and revision. A total of 23 key questions and relevant outcomes were selected and rated by the experts using an online survey tool. We developed a special literature review strategy and protocol and implemented them on May 15, 2020, with subsequent evaluation of the publications identified by 2 independent reviewers, who then extracted eligible data. After 2 screening phases, 21 studies fulfilling the inclusion criteria were retained. Subsequently the quality of the evidence following GRADE using the GRADEpro guideline development tool (Table I) was assessed.[3,5,7-9]

Modified evidence-to-decision (EtD) frameworks were used to assist in judging the size of the desirable and the undesirable effects and the balance between these effects, which provided an overview of quality. A recommendation for each evidence-based key question was drafted using standardized wording.

In a preconference online voting round, all GRADE tables, EtD frameworks, and draft recommendations were presented and voted on. The results were either fed back to the expert panel or integrated into the EtD frameworks. All EtD frameworks and draft recommendations were made available to the participants before the consensus conference. In none of the cases was a substantial conflict of interest (high economic or dependency on companies involved in urticaria treatment) observed.[5]

During the conference, all recommendations were voted on electronically by the participants, all of whom had to submit a declaration that they were a urticaria specialist seeing patients on a regular basis and report any conflicts of interest. A nominal group technique was used to achieve consensus on the different recommendations.[3,5,8]

A strong consensus was defined as more than 90% agreement, whereas 70% to 89% agreement was considered consensus. All recommendations had to pass with a 75% agreement.

DEFINITION AND CLASSIFICATION OF URTICARIA

The definitions of acute urticaria (ie, ≤6 weeks in duration) and chronic urticaria (CU) (ie, >6 weeks in duration) do not differ between the current and previous versions of the international urticaria guideline.[4,10,11] Also, the current and previous versions agree that urticaria is defined by itchy wheals (typically with surrounding erythema and resolution within 24 hours), angioedema (defined as a deeper swelling lasting up to 72 hours), or both. Thus, the classification of urticaria (Table II) remains unchanged. This reflects the fact that urticaria experts continue to agree that urticaria can manifest with stand-alone angioedema (ie, with angioedema without wheals). However, it should be noted that although angioedema is not clinically distinguishable from the angioedema seen in patients with hives, the inflammatory markers are not the same (eg, IgG anti-FcεRI, and female predominance is low).[12] Before urticaria is diagnosed in patients with angioedema without wheals, other diseases that come with angioedema, especially bradykinin-mediated angioedema, must be excluded (Fig 1[4,10]). Also, further studies are needed and encourage better understanding of the similarities and differences between urticaria that manifests with wheals, angioedema with wheals but no angioedema, and angioedema without wheals.

TABLE I. Summary of the GRADE approach to assessing the quality of evidence by outcome

Grade	Definition of grade
High (++++)	We are very confident that the true effect lies close to that of the estimate of effect
Moderate (+++)	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Low (++)	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect
Very low (+)	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

TABLE II. Classification of CU in the current version of the international urticaria guideline

CSU	Chronic inducible urticaria
Spontaneous appearance of wheals, angioedema, or both owing to known or unknown causes for >6 weeks	Symptomatic dermographism Cold urticaria Delayed pressure urticaria Solar urticaria Heat urticaria Vibratory angioedema Cholinergic urticaria Contact urticaria Aquagenic urticaria

ASSESSMENT OF DISEASE ACTIVITY, IMPACT, AND CONTROL IN PATIENTS WITH CU

In this area, the newest version of the international urticaria guideline is more precise and comprehensive than previous versions. It emphasizes the importance of consistent and continued assessment of patients with CU for their disease activity, quality of life (QoL) impairment, and disease control. It also newly recommends basing management decisions on the results of these assessments, most importantly, disease control measurements.

The most recent version of the international urticaria guideline explicitly says that patients should be assessed for disease activity, impact, and control at the first and every follow-up visit. It also recommends 6 instruments for doing so; all of them are validated patient-reported outcome measures (PROMs) that are available in many languages and free of charge for use in clinical practice.

Like previous versions, the current urticaria guideline says that the 7-Day Urticaria Activity Score (Table III) should be used to determine disease activity and response to treatment in patients

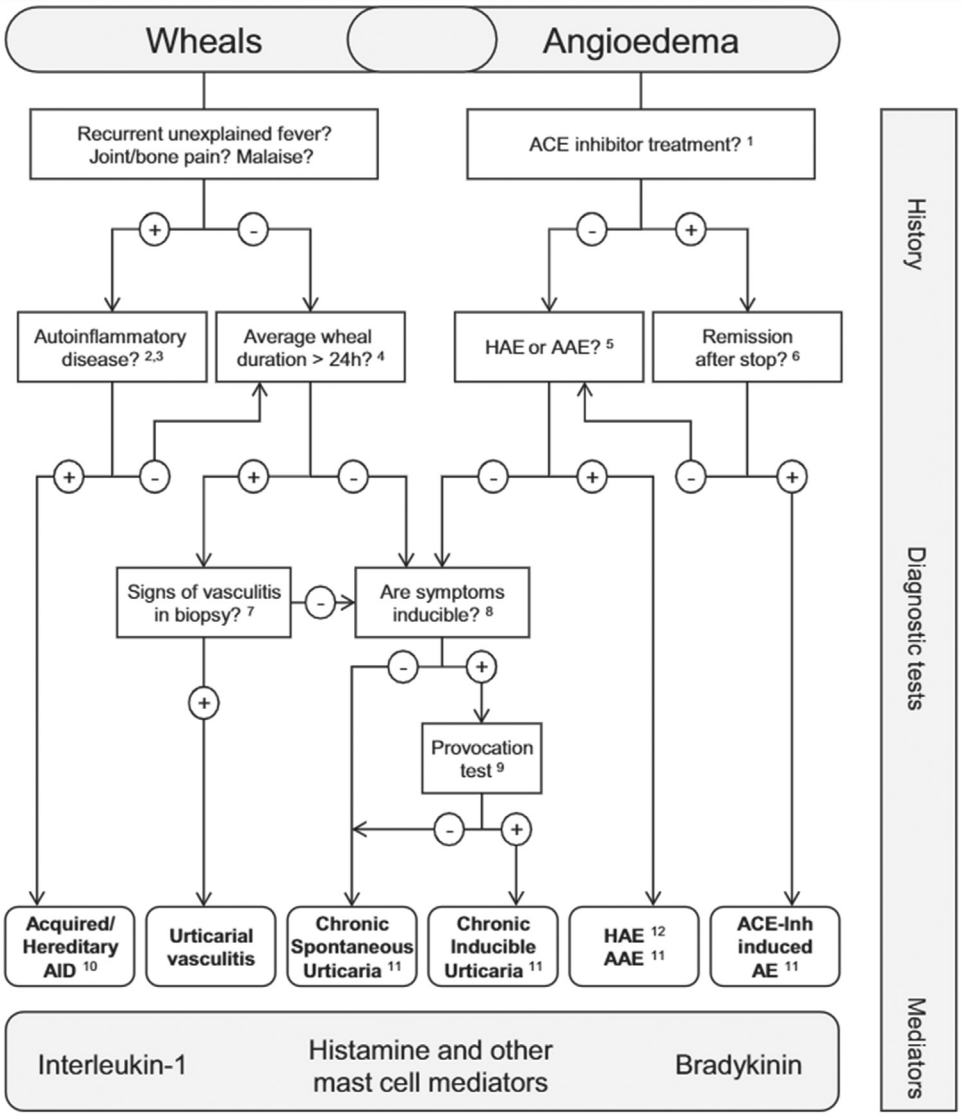
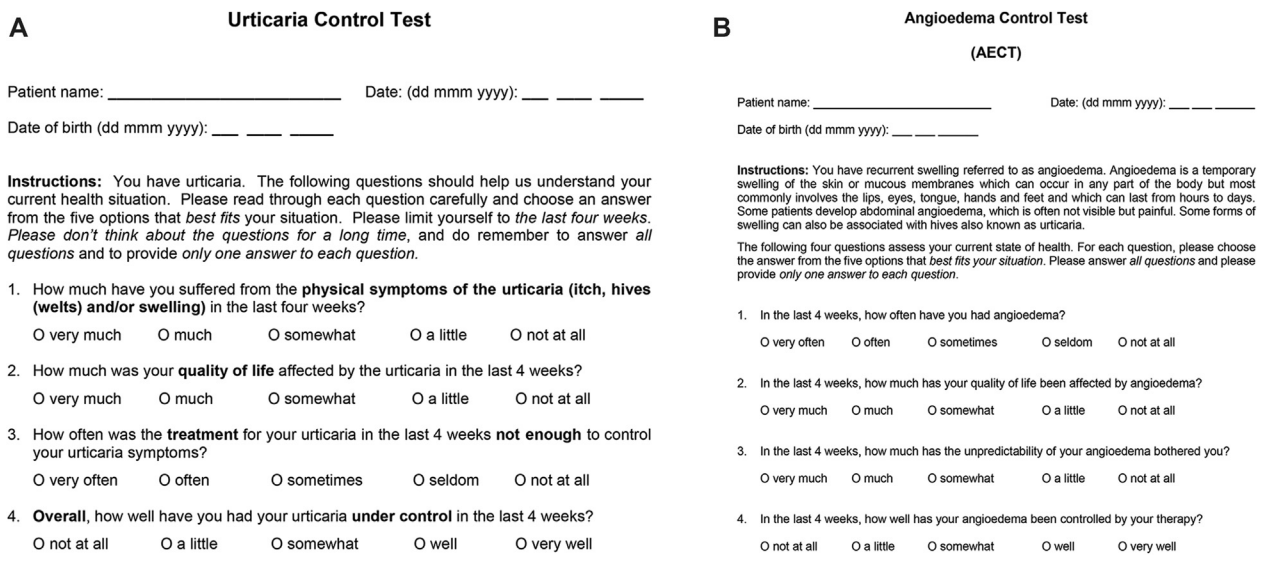


FIG 1. Recommended diagnostic algorithm for CU (for patients presenting with wheals and/or angioedema [AE] for >6 weeks]). [1]In addition to angiotensin-converting enzyme (ACE) inhibitors (ACE-Inhs), angiotensin II type 1 receptor blockers (sartans), dipeptidyl peptidase IV inhibitors (gliptins), and neprilysin inhibitors have been described as inducing angioedema, but much less frequently. [2]Patients should be asked for a detailed family history and age of disease onset. [3]Test for elevated inflammation markers (C-reactive protein level and erythrocyte sedimentation rate), test for paraproteinemia in adults, look for signs of neutrophil-rich infiltrates in skin biopsy specimens, and perform gene mutation analysis for hereditary periodic fever syndromes (eg, cryopyrin- associated periodic syndrome), if strongly suspected. [4]Patients should be asked, "For how long does each individual wheal last?" [5]Test for complement C4, C1-INH levels and function; in addition, test for C1q and C1-INH antibodies if acquired angioedema (AAE) is suspected; and perform gene mutation analysis if the results of the aforementioned tests are unremarkable but the patient's history suggests hereditary angioedema (HAE). [6]Remission should occur within a few days, and in rare cases up to 6 months of ACE inhibitor discontinuation. [7]Does the biopsy specimen of lesional skin show damage to the small vessels in the papillary and reticular dermis and/or fibrinoid deposits in perivascular and interstitial locations suggestive of urticarial vasculitis? [8]Patients should be asked, "Can you make your wheals appear? Can you bring out your wheals?" [9]In patients with a history suggestive of inducible urticaria, standardized provocation testing according to international consensus recommendation 45 should be performed. [10]Acquired autoinflammatory syndromes include Schnitzler syndrome as well, as systemic-onset juvenile idiopathic arthritis (sJIA) and adult-onset Still disease; hereditary autoinflammatory syndromes include cryopyrin-associated periodic syndromes (CAPS) such as familial cold autoinflammatory syndromes (FCAS), Muckle-Wells syndrome (MWS), neonatal-onset multisystem inflammatory disease (NOMID), aznd more rarely hyper-IgD syndrome (HIDS) and TNF-α–associated periodic syndrome (TRAPS). [11]In some rare cases, recurrent angioedema is neither mast cell mediator–mediated nor bradykinin-mediated, and the underlying pathomechanisms remain unknown. These rare cases are referred to as idiopathic angioedema by some authors. [12]Several subtypes of HAE are known: hereditary angioedema due to C1-inhibitor deficiency (HAE-1); hereditary angioedema due to C1-inhibitor dysfunction (HAE-2); hereditary angioedema with normal C1-inhibitor levels (HAE nC1-INH) due to a mutation in factor 12 (FXII), angiopoietin-1 (ANGPT1), PLG plasminogen (PLG), kininogen (KNG1), myoferlin (MYOF), and (heparan sulfate-glucosamine 3- O-sulfotransferase 6 (HS3ST6) or some unknown factor. *AID*, Autoinflammatory disease.

TABLE III. The 7-Day Urticaria Activity Score for assessing disease activity in CSU

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals per 24 h)	Mild (present but is not annoying or troublesome)
2	Moderate (20-50 wheals per 24 h)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (>50 wheals per 24 h or large confluent areas of wheals)	Intense (severe pruritus that is sufficiently troublesome to interfere with normal daily activity or sleep)

Sum of scores: Scores of 0 to 6 points for each day can be summarized over the course of 1 week (for a maximum total score of 42 points) to yield the 7-Day Urticaria Activity Score weekly score.



A

Urticaria Control Test

Patient name: _____ Date: (dd mmm yyyy): ___ ___ ____

Date of birth (dd mmm yyyy): ___ ___ ____

Instructions: You have urticaria. The following questions should help us understand your current health situation. Please read through each question carefully and choose an answer from the five options that *best fits* your situation. Please limit yourself to *the last four weeks. Please don't think about the questions for a long time*, and do remember to answer *all questions* and to provide *only one answer to each question.*

1. How much have you suffered from the **physical symptoms of the urticaria (itch, hives (welts) and/or swelling)** in the last four weeks?
   O very much O much O somewhat O a little O not at all
2. How much was your **quality of life** affected by the urticaria in the last 4 weeks?
   O very much O much O somewhat O a little O not at all
3. How often was the **treatment** for your urticaria in the last 4 weeks **not enough** to control your urticaria symptoms?
   O very often O often O sometimes O seldom O not at all
4. **Overall**, how well have you had your urticaria **under control** in the last 4 weeks?
   O not at all O a little O somewhat O well O very well

B

Angioedema Control Test

(AECT)

Patient name: _____ Date: (dd mmm yyyy): ___ ___ ____

Date of birth (dd mmm yyyy): ___ ___ ____

Instructions: You have recurrent swelling referred to as angioedema. Angioedema is a temporary swelling of the skin or mucous membranes which can occur in any part of the body but most commonly involves the lips, eyes, tongue, hands and feet and which can last from hours to days. Some patients develop abdominal angioedema, which is often not visible but painful. Some forms of swelling can also be associated with hives also known as urticaria.

The following four questions assess your current state of health. For each question, please choose the answer from the five options that *best fits your situation*. Please answer *all questions* and please provide *only one answer to each question.*

1. In the last 4 weeks, how often have you had angioedema?
   O very often O often O sometimes O seldom O not at all
2. In the last 4 weeks, how much has your quality of life been affected by angioedema?
   O very much O much O somewhat O a little O not at all
3. In the last 4 weeks, how much has the unpredictability of your angioedema bothered you?
   O very much O much O somewhat O a little O not at all
4. In the last 4 weeks, how well has your angioedema been controlled by your therapy?
   O not at all O a little O somewhat O well O very well

FIG 2. The UCT **(A)** and AECT **(B)**. Reprinted with permission from MOXIE GmbH, Berlin, Germany (www.moxie-gmbh.de).

with chronic spontaneous urticaria (CSU). For patients with CSU with angioedema, with or without wheals, the Angioedema Activity Score should be used. Those patients with CSU who experience wheals and angioedema should use the 7-Day Urticaria Activity Score and the Angioedema Activity Score in combination. Also unchanged is the recommendation to use the Chronic Urticaria Quality of Life (CU-Q2oL) questionnaire to determine QoL impairment in patients with CSU with wheals, the Angioedema Urticaria Quality of Life questionnaire for patients with CSU with angioedema with or without wheals, and both instruments for patients with CSU with wheals and angioedema.

Importantly, where the current version of the guideline differs from previous ones is in its approach to assessing disease control. It still recommends use of the Urticaria Control Test (UCT) (Fig 2, *A*) by patients with CSU who develop wheals with or without angioedema, as did the previous guideline version. However, it is now recommended that patients with CSU who develop angioedema with or without wheals use the Angioedema Control Test (AECT) (Fig 2, *B*), and patients with CSU with wheals and angioedema use the UCT and the AECT.

The UCT, a validated instrument for measuring disease control in all forms of CU (CSU and chronic inducible urticaria), has 4 questions, with 5 answer options each, and a clearly defined cutoff for patients with well-controlled versus poorly controlled disease (ie, 12 points). The AECT is similar to the UCT in how it works and is used; however, it quantifies disease control in patients with CSU with angioedema and patients with other forms of recurrent angioedema. Two versions of the AECT exist, one with a 4-week recall period and the other with a 3-month recall period. Its cutoff for well-controlled disease is 10 points. Both the UCT and the AECT are easy to administer, and the score should be used to guide treatment decisions.

The current version of the guideline emphasizes that the first and most important treatment aim in CU is to provide patients with complete control of their disease. In most patients, this requires 1 or more changes in treatment, which is in line with the guideline algorithm (which should be implemented on the basis of the results of the UCT).[13]

DIAGNOSTIC TESTING

All versions of the international guideline, including the most recent one, recommend no routine testing in acute urticaria unless the patient's history suggests an underlying cause that requires specific testing to confirm an allergic cause.[4,10]

Also, for chronic inducible urticaria, no changes were made in the updated guideline, with testing limited to confirmation of the diagnosis by provocation testing and subsequent trigger threshold assessment. Thus, having appropriate testing protocols and instruments in place remains important.[4,10,14,15]

Regarding the diagnostic workup of CSU, the previous version recommended only very limited routine laboratory testing. The

TABLE IV. The aims of the diagnostic workup in every patient with CSU

Step	Action
History	Physical examination,* basic tests,† and UCT
Confirmation	Rule out differential diagnoses
Cofactors	Look for indicators of CSU^{aiTI} or CSU^{aiTIIb}
Comorbidities	Identify potential triggers and aggravators
Consequences	For example, check for CIndU, autoimmunity, and mental health
Components	For example, identify problems with sleep, distress, sexual health, and social performance
Course	Monitor CSU activity, impact, control

Data from Metz et al.[16]
CIndU, Chronic inducible urticaria; CSU^{aiTI}, type I autoimmune CSU; CSU^{aiIIb}, type IIb autoimmune CSU.
*Including a review of patient photo documentation.
†Differential blood count, C-reactive protein level/erythrocyte sedimentation rate, IgG–anti-TPO level, and total IgE level for patients with special care.

current version of the international urticaria guideline provides more comprehensive and detailed guidance. First, it stresses the point that the diagnostic workup of CSU has several aims, collectively referred to them as the 7 *C*s (Table IV)[16]: (1) confirm the diagnosis and exclude differential diagnoses; (2) look for the underlying causes; (3) identify relevant conditions that modify disease activity; (4) check for comorbidities; (5) check for consequences of CSU; (6) assess predictors of the course of disease and response to treatment; and (7) monitor disease activity, impact, and control. To this end, the diagnostic workup includes a thorough history, physical examination (including review of pictures of wheals and/or angioedema), the use of PROMs, and basic tests (including a differential blood count and measurement of C-reactive protein level and/or ESR and total IgE and IgG–anti-thyroid peroxidase [TPO] levels). The latter 2 are and were added on the basis of recent evidence that CSU can be due to autoallergic or autoimmune-mediated skin mast cell activation,[17] with IgE autoantibodies to self-antigens in autoallergic CSU and mast cell–directed activating IgG or IgM autoantibodies in autoimmune CSU.[18,19] Testing for IgG–anti-TPO and total IgE levels can help to bring more clarity regarding why patients have CSU. Patients with autoimmune CSU are more likely to have low or very low total IgE levels and elevated levels of IgG–anti-TPO IgG.[18-20] A high ratio of IgG–anti-TPO to total IgE is currently the best surrogate marker for autoimmune CSU.[18] In addition, a CU index should be obtained in patients who are not responsive to H1 antihistamines to determine whether they have antibodies directed against IgE, FcεRI, or anti-FcεRII or an alternate histamine-releasing factor. These biomarkers have also been reported to be prognosticators for treatment outcomes with omalizumab or immunosuppressants such as cyclosporin. Also, the autologous serum test is suggested as an additional procedure for the diagnosis of an auto-reactive form of the disease, but the relevance is not very high, as omalizumab works independently of the autologous serum test. On the basis of the results obtained by basic tests, history, physical examination, and PROMs, further diagnostic testing may be performed as indicated.

MANAGEMENT

The most important change that the recent version of the international urticaria guideline brings to the management of urticaria is its recommended approach to pharmacologic treatment. Here, 2 points are important.

First, the recommended treatment algorithm was streamlined, and it now features 3 steps instead of 4. The recommendations for the use of first-line treatment (antihistamine), second-line treatment (omalizumab), and third-line treatment (cyclosporine) now include guidance on updosing and duration (Fig 3, *A* and *B*). For omalizumab, for example, the recommendation is to start treatment with 300 mg every 4 weeks, based on well-designed robust double-blind placebo-controlled studies demonstrating its efficacy in CSU.[21,22] In patients with insufficient response, updosing should be considered; it can be done by shortening the interval and/or increasing the dosage. Several studies have shown that this can be of benefit in individual cases, especially in patients with a high body mass index.[23,24] The maximum recommended dose of omalizumab is 600 mg every 14 days, and up to 6 months should be allowed for patients to respond to omalizumab. The recommendation to use higher than standard doses of omalizumab, if needed, is based on real-life experience with CSU and clinical trials in asthma, in which the safety of higher doses was shown to have a spectrum and frequency of adverse events similar to those observed with 300 mg every 4 weeks.[25] The risk-benefit profile of high-dose omalizumab is superior to that of cyclosporine, which should be considered for the treatment of patients who do not respond to higher than standard doses of omalizumab. Treatment of urticaria with cyclosporine has shown positive outcomes in case studies and clinical studies, including double blind placebo-controlled studies.[26-28] Even long-term low-dose treatment with cyclosporine has been shown to be safe and successful in a small group of patients.[29] It should be noted, however, that there are potential risks associated with cyclosporine, including the risk of hypertension, epilepsy in those predisposed, hirsutism, gum hypertrophy, and renal failure. It is also advised that blood pressure and renal function (blood urea nitrogen and creatinine levels) be monitored every 6 weeks while the patient is receiving cyclosporine.[30]

Second, the latest update of the international urticaria guideline asks physicians to use an "as much as needed and as little as possible" approach, by stepping up and stepping down the treatment of CU, based on levels of disease control assessed with the UCT. In patients who are treated with a standard-dosed second-generation antihistamine and whose CU cannot be completely controlled (ie, those with a UCT score of 16), a higher dose (up to 4-fold higher) should be used. In patients with complete disease control, step-down should be considered to reduce the treatment burden and assess patients for spontaneous remission. Step-down protocols should bring on board individual patient needs and, in general, be implemented with prudence and patience. For example, patients should not step down a higher than standard–dosed antihistamine before completing at least 3 consecutive months of complete control, and the daily dose should not be reduced by more than 1 tablet per month. When control is lost during treatment step-down (ie, when patients develop breakthrough signs and symptoms following dose reduction), the antihistamine should be used at the last dose that previously provided complete control.[13]

CONCLUSION AND OUTLOOK

CU is frequent.[31] It has a significant impact on quality of life and places a substantial economic burden on our health care

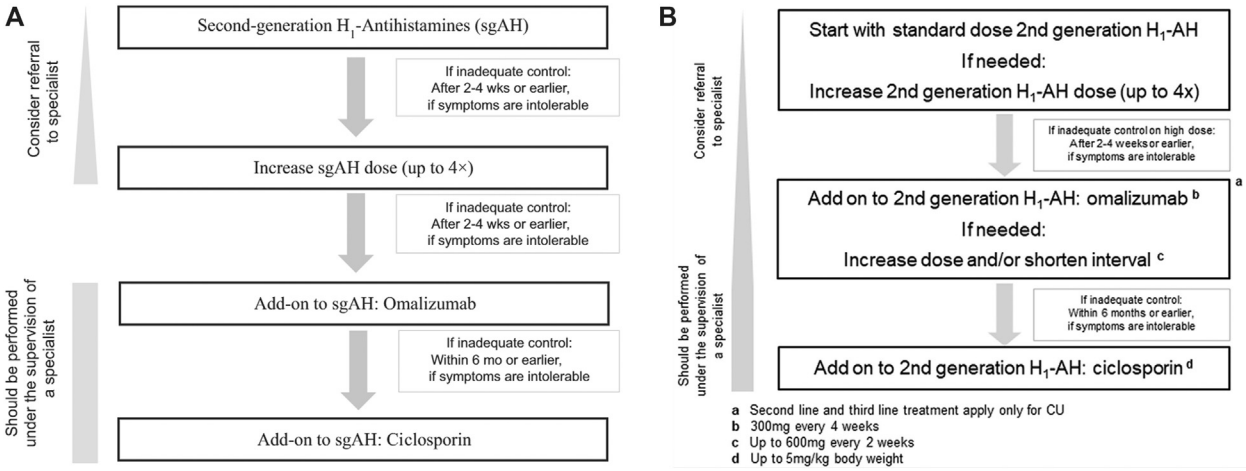


FIG 3. Comparison of the treatment algorithms of the old (**A**) and new (**B**) versions of the international urticaria guideline. *fgAH*, First-generation antihistamine; *H1-AH*, H1 antihistamine; *LTRA*, leukotriene receptor antagonist; *sgAH*, second-generation antihistamine.

systems.[32] Therefore, it is essential that experts critically analyze the existing literature and pool their experience to provide guidance to clinicians on how to best manage this condition in an efficient and cost-effective manner. The most recent update and revision of the international urticaria guideline does this with important changes in the recommendations versus those in the previous version. The plan is to start the next update and revision of this guideline in 2023, with an open call for participation posted on the website of the Global Asthma and Allergy European Network (GA^{2}LEN) network of urticaria centers of reference and excellence, Urticaria Centers of Reference and Excellence (www.ga2len-ucare.com).[33] Publication of the next update and revision is expected in 2026. A topic for future discussion is the use of additional diagnostic procedures, such as the basophil activation test, which should be performed in patients who are not responsive to H1 antihistamines to determine whether they have antibodies directed against IgE, FcεRI, or anti-FcεRII or an alternate histamine-releasing factor. These biomarkers have also been reported to be prognosticators for outcomes of treatment with omalizumab or immunosuppressants such as cyclosporine. Until then, the current version of the guideline should be implemented in routine clinical practice. Urticaria research should address unanswered questions and provide further insights that will guide development of the next and improved version of the international urticaria guideline.

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