

A Comparison of the United States and International Perspective on Chronic Urticaria Guidelines



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Urticaria is a heterogeneous skin disorder that may be acute or chronic and is defined by the appearance of wheals, angioedema, or both. The European perspective is expressed in a recent international guideline and the American perspective has been based on the US Joint Task Force chronic urticaria practice parameter published in 2014. Both the international guideline (initiated by the European societies European Academy of Allergology and Clinical Immunology [EAACI]/Global Allergy and Asthma European Network [GA²LEN]/European Dermatology Forum [EDF] in collaboration with the World Allergy Organization [WAO]) and the US (American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology) guideline have been developed to help direct primary care physicians and specialists in the management of their patients with urticaria. The EAACI/GA²LEN/EDF/WAO guideline applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to developing consensus recommendations and these were then discussed in a Delphi conference including more than 250 specialists in the field and have been endorsed by more than 40 international societies. In contrast, the US Joint Task Force CU practice

parameter made recommendations based on scientific evidence whenever possible; however, when there was insufficient evidence, recommendations were based on expert consensus opinion. Although both agree on most points regarding the definition, general evaluation, and treatment, there are some differences that exist between the 2 guidelines. Most of these differences pertain to recommendations based on expert opinion because of weak scientific evidence. Within this document, we compare the recommendations of these 2 groups, highlighting the key similarities and differences. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1144-51)

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INTRODUCTION

In 2000 the first European guideline based on a consensus conference was developed.^{1,2} In December 2016, the fifth conference was organized to create an international, global guideline. Initiated by the European Academy of Allergology and Clinical Immunology in conjunction with the European Dermatology Forum, the Global Allergy and Asthma European Network, and the World Allergy Organization, all international societies were invited to participate.^{3,4} A driving force behind the idea of the development of this guideline was to achieve a worldwide consensus on the principles of classification, diagnosis, and treatment of urticaria, which could subsequently be adapted by urticaria experts in different regions of the world through the involved parent organization. Altogether, 42 allergy/dermatology national and international societies representing 94 countries participated in the updated guideline. The North American and South American societies included were the American Academy of Allergy, Asthma & Immunology (AAAAI), the American Academy of Dermatology, the American College of Allergy, Asthma and Immunology (ACAAI), the Brazilian Association of Allergy and Immunopathology, the Mexican College of Clinical Immunology and Allergy, the Canadian Society of Allergy and Clinical Immunology, the Brazilian Society of Dermatology, and the Latin American Society of Allergy and Immunology.^{3,4} In this review, we therefore refer to it as an international guideline.

Unique to all current urticaria guidelines, the international urticaria guideline has used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which is considered the most rigorous and comprehensive methodology for scientific evidence-based guidelines.⁵ The guideline was prepared by a panel consisting of delegates of each

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Abbreviations used

CSU-chronic spontaneous urticaria

involved society, which culminated with a large Delphi conference held in Berlin, Germany, including the participation of more than 250 urticaria specialists from all over the world, resulting in the final recommendations that achieved a large global consensus. It was subsequently fully endorsed by the American Academy of Dermatology and the ACAAI and conditionally endorsed by the AAAAI.^{3,4}

Although the United States Joint Task Force Urticaria guideline (referred to as the US guideline in this review) published in 2014⁵ shares many of the same recommendations as the international guideline, there are several key differences that will be highlighted in this review.⁴⁻⁶

METHODOLOGIES USED FOR GENERATING THE INTERNATIONAL AND US GUIDELINES

The updated revised international guideline takes into account the Appraisal of Guidelines Research and Evaluation instrument and the methods suggested by the GRADE working group. The literature review was conducted using the methods given in the Cochrane Handbook for Systematic Reviews of Interventions.^{3,7}

Experts from 42 societies were nominated to be involved in the development of the guideline. Initially, key questions and relevant outcomes were selected and rated by the experts using an online survey tool and 23 key questions were identified. A special literature review protocol was developed that specified the literature search strategy. The literature review was conducted on June 1, 2016, and evaluated by 2 independent reviewers who extracted eligible data. After 2 screening phases, 65 studies fulfilling the inclusion criteria were retained. Subsequently, the quality of the evidence following GRADE using GRADEpro Guideline Development Tool (Table I) was assessed.^{3,8,9}

Modified evidence-to-decisions (EtD) frameworks were used to assist in judging the size of the desirable and 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.³

During the conference, all recommendations were voted on by more than 250 participants, all of whom had to submit a declaration that they were an urticaria specialist seeing patients on a regular basis and whether or not they had any conflicts of interest. A nominal group technique was used to achieve consensus on the different recommendations.^{3,10}

The consensus conference followed a structured approach, which included presentation of the evidence and draft recommendation, open discussion, initial voting, or collection of alternative wording followed by final voting, if necessary. Voting results were recorded. A strong consensus was defined as more than 90% agreement, whereas 70% to 89% was considered

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

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 the 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 the 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

consensus. All recommendations passed with a 75% agreement. An internal and an external review of this process took place. The internal review included the involvement of an international methodologist, supervising the process, and an external review of the manuscript by additional members of all societies involved on the basis of their institutional and national regulations (eg, licensing status of the recommended medication or availability). For example, in the case of the European Dermatology Forum, the review board consisted of 41 members.³

In contrast, the Joint Task Force practice parameter on chronic urticaria conducted an extensive medical literature search for various terms that were considered relevant to this topic. Literature searches were performed on PubMed, Google Scholar, and the Cochrane Database of Systematic Reviews. All reference types were initially included in the results and references identified as relevant were further searched for relevant references within each article. After acquiring these articles, any relevant references were again searched for and if novel were included in the parameter. In addition, members of the workgroup were asked to provide any references that may have been missed by this initial search. Published clinical studies were rated by category of evidence, which was used to establish the strength of the recommendations. The parameter was subsequently reviewed by designated experts by the AAAAI and the ACAAI. After responding to queries and comments by these reviewers and incorporating changes into the document, the parameter was posted on an open website for all members of the AAAAI and the ACAAI to review and make comments. These comments were responded to by the working group point by point and the parameter was again updated to include any relevant changes or clarifications. Based on this rigorous process, the parameter was believed to represent an evidence-based, broadly accepted consensus document.⁵

DEFINITION AND CLASSIFICATION

Definitions of acute and chronic urticaria do not differ between the guidelines.⁴⁻⁶ Both agree that less than 6 weeks is acute and more than 6 weeks is chronic urticaria. In general, they define urticaria as the presence of sudden appearance of wheals (with central swelling and surrounding erythema, which are typically pruritic and resolve within about 24 hours) with or without angioedema, defined as a deeper swelling lasting up to 72 hours. Wheals lasting longer than 24 to 48 hours, those that leave hyperpigmentation, or lesions that burn may be vasculitic

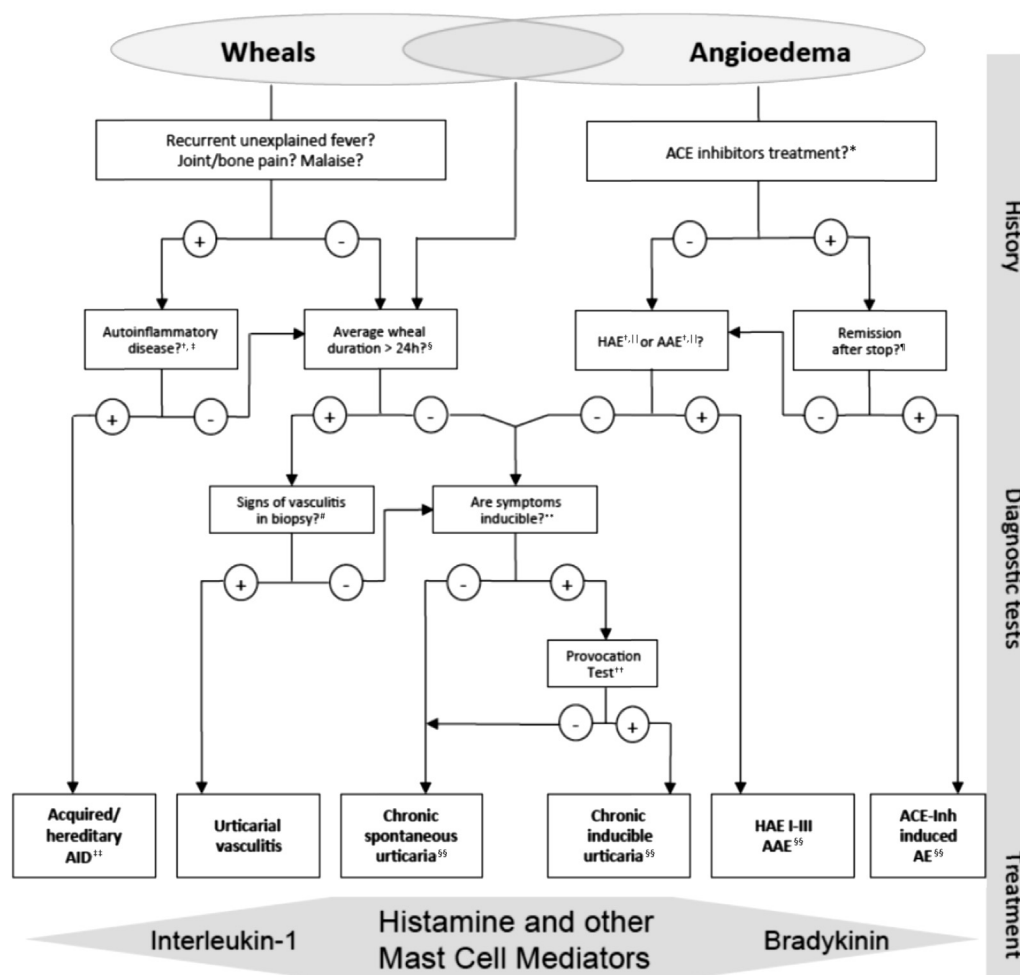


FIGURE 1. Diagnostic algorithm for patients presenting with wheals, angioedema, or both. *AAE*, Acquired angioedema due to C1-inhibitor deficiency; *ACE-Inh*, angiotensin-converting enzyme inhibitor; *AE*, angioedema; *AID*, autoinflammatory disease; *HAE*, hereditary angioedema; *RAS*, renin-angiotensin system. * Apart from ACE inhibitors other renin inhibitors and sartans have been described to induce angioedema but much less frequently. † Patients should be asked for a detailed family history and age of disease onset. ‡ Test for elevated inflammation markers (C-reactive protein, erythrocyte sedimentation rate), test for paraproteinemia in adults, look for signs of neutrophil-rich infiltrates in skin biopsy; perform gene mutation analysis for hereditary periodic fever syndromes (eg, Cryopyrin-associated periodic syndrome), if strongly suspected. § Patients should be asked: "For how long does each individual wheal last?" || Test for complement C4, C1-INH levels and function; in addition, test for C1q and C1-INH antibodies, if AAE is suspected; do gene mutation analysis, if former tests are unremarkable but patient's history suggests hereditary angioedema. ¶ If there is no remission after 6 mo of ACE-inhibitor discontinuation, C1-inhibitor should be tested for. # Does the biopsy of lesional skin show damage of the small vessels in the papillary and reticular dermis and/or fibrinoid deposits in perivascular and interstitial locations suggestive of urticarial vasculitis? ** Patients should be asked: "Can you make your wheals come? Can you bring out your wheals?" †† In patients with a history suggestive of inducible urticaria, standardized provocation testing according to international consensus recommendations¹¹ should be performed. ‡‡ 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 such as familial cold autoinflammatory syndromes, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease, more rarely hyper-IgD syndrome and TNF receptor alpha-associated periodic syndrome (TRAPS). §§ 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.

rather than urticarial and skin biopsy for routine hematoxylin and eosin or if appropriate immunofluorescence staining or special staining for mast cells may be necessary to differentiate between these and other disorders.^{4,5}

Both the international and the US guideline include angioedema in the definition of urticaria because wheals and

angioedema have similar pathophysiology and exist in the same spectrum of disease.^{4,5} Figure 1 is¹¹ the diagnostic algorithmic approach proposed by the international guideline that incorporates all forms of urticaria and angioedema.⁴

Typically, urticaria is generally a self-limiting innocuous condition but can present with systemic symptoms, associated

with anaphylaxis manifesting as angioedema of the tongue or throat, and gastrointestinal and/or respiratory symptoms.² Both guidelines emphasize the importance of differentiating acute urticaria from anaphylaxis because the latter may require emergency treatment including the administration of epinephrine.^{4,5}

The parameters differ with respect to classification terminology. The international guideline uses the term “spontaneous” to indicate that no eliciting factor is involved and “inducible” to indicate that a specific eliciting factor is involved (Table II). Inducible urticaria replaces the term physical urticaria, the term advocated by the US guideline, which has been used to describe the random occurrence of urticaria and hives secondary to physical and/or emotional factors. The international guideline uses the term “persistent” and “intermittent,” whereas the US parameter uses the terms “continuous” or “intermittent.” For inducible or physical hives, both guidelines provide detail regarding the differing appearances of urticaria as well as the techniques used to establish a diagnosis. Furthermore, both documents use the term “idiopathic” but emphasize that the term chronic idiopathic urticaria should not be immediately used to characterize any patient presenting with chronic urticaria until potential causes have been adequately excluded.^{4,5} Finally, the international guidelines use the term “autoimmune” urticaria, whereas the US guidelines recommend “autoantibody-associated” urticaria because FcER1 alpha subunit antibodies and other autoantibodies (antinuclear antibodies, rheumatoid factor, thyroid autoantibodies...) are associated with chronic spontaneous urticaria (CSU) but have not been mechanistically confirmed as causative of CSU.

CONTROL AND QUALITY OF LIFE

Acute and chronic urticaria affect up to 20% and 5% of the general population, respectively, and these conditions can have a significant impact on patient quality of life. The international guidelines specifically addresses control and quality of life in acute and chronic urticaria, advocating several validated instruments that should be used at each patient visit.⁴ The urticaria control test activity score is a validated scoring system that has been previously used in randomized clinical drug trials that measures both pruritus (0-3 score) and the number of wheals (0-3 score assigned on the basis of number of wheals) to create a total score ranging from 0 to 6. The scores are summed over a 24-hour period for 7 consecutive days to yield a possible total score ranging from 0 to 42, which is referred to as the UAS7 (Table III).¹² The Urticaria Control Test is a simple 4-question instrument where each question is ranked from 0 to 5 on the basis of severity, with a total possible score of 20.¹³ Finally, the Chronic Urticaria Quality of Life (CU-Q2oL) is another instrument validated in multiple languages that assesses severity of chronic urticaria quality-of-life impairment.¹⁴ The US practice parameter does not specifically recommend 1 or more control or quality-of-life instruments because at the time of publication they had not been adequately validated. However, the guideline did recommend obtaining an objective assessment of itch severity (ie, an itch severity score) and a quantifiable percentage of the body covered in hives each day (ie, a visual analogue scale) to assess the severity of hives and response to treatment.^{5,6}

DIAGNOSTIC TESTING

Both guidelines recommend no routine testing in acute urticaria unless the history suggests an underlying cause that requires

TABLE II. Classification of urticaria in the international guideline

Chronic urticaria subtypes	
Chronic spontaneous urticaria (CSU)	Inducible urticaria
Spontaneous appearance of wheals, angioedema, or both for >6 wk due to known* or unknown causes	Symptomatic dermographism† Cold urticaria‡ Delayed pressure urticaria§ Solar urticaria Heat urticaria Vibratory angioedema Cholinergic urticaria Contact urticaria Aquagenic urticaria

*For example, autoreactivity, ie, the presence of mast cell–activating autoantibodies.

†Also called *urticaria factitia* or dermographic urticaria.

‡Also called cold contact urticaria.

§Also called pressure urticaria.

||Also called heat contact urticaria.

TABLE III. The urticaria activity score (UAS7) for assessing disease activity in CSU

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

Sum of score: 0-6 for each day is summarized over 1 wk (maximum 42).

specific testing to confirm a specific trigger or potential cause noted through the review of systems.^{4,5}

For inducible urticaria, both guidelines advocate provocation testing to confirm the suspected cause and when possible, the international guidelines advocate further identifying the threshold response of the inducible trigger. This later recommendation is dependent on facilities having the proper instruments that can measure these threshold responses, which is often thwarted because of their underlying cost.^{4,5,15,16} Furthermore, a recent meta-analysis found insufficient well-designed studies to support the diagnostic utility of office provocation for inducible urticaria.¹⁵ There is consensus that an accurate diagnosis of inducible urticaria is desirable in order to develop precision treatment recommendations for these heterogeneous conditions especially when one considers that the prognosis/outcome of chronic urticaria is poorer in the presence of an inducible urticaria component.^{4,5,17} However, additional studies are needed to validate whether these provocation tests can reproducibly elicit each form of inducible urticaria and that threshold changes in response to these provocation responses pretreatment and posttreatment can be demonstrated.

Regarding the diagnostic workup of CSU, both the US and international guidelines have recommended limited routine laboratory testing, which includes a complete blood cell count with differential, western sedimentation rate, and/or C-reactive protein. However, both guidelines emphasize that additional

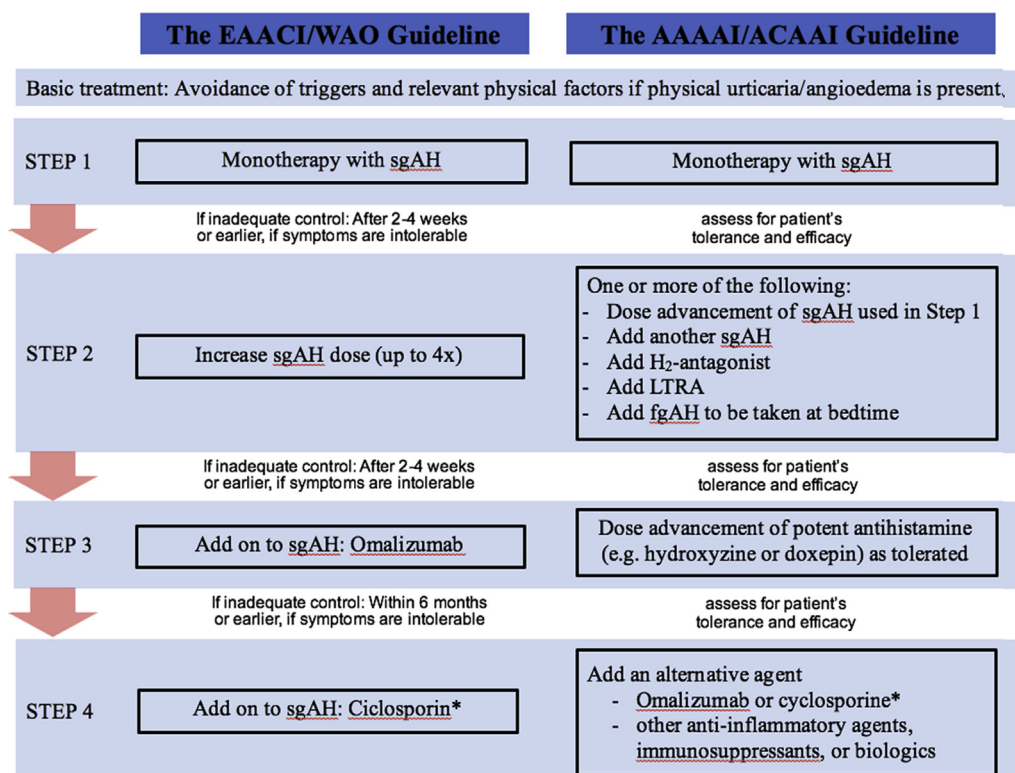


FIGURE 2. Comparison of treatment algorithms of the international and US guidelines. EAACI, European Academy of Allergology and Clinical Immunology; fgAH, first-generation antihistamine; LTRA, leukotriene receptor antagonist; sgAH, second-generation antihistamine; WAO, World Allergy Organization. *Different spellings as used in the respective guideline. Additional comments: EAACI/WAO: A short course of corticosteroids may be considered in case of severe exacerbation. AAAAI/ACAAI: Begin treatment at step appropriate for patient's level of severity and treatment history; "step-down" treatment is appropriate at any step, once consistent control of urticaria/angioedema is achieved.

testing may be appropriate on the basis of either the patient's history or the clinician's suspicion for an existing underlying cause.^{4,5}

The underlying cause of CSU is still unknown. Over the past 2 decades, there have been many studies demonstrating the strong association of thyroid, connective tissue, and FcεR1 alpha subunit antibodies in patients with CSU compared with the general population.^{18,19} However, the clinical relevance of these antibodies has remained elusive because current therapies such as omalizumab seem to work regardless of whether or not patients manifest these autoantibodies.²⁰ Work is ongoing to better understand their relevance in the pathogenesis of CSU but as a result neither guideline has recommended performing a routine autologous serum or plasma skin test, a chronic urticaria index, or basophil activation test, or obtaining autoantibodies for thyroid disease, systemic lupus erythematosus, rheumatoid arthritis, or other connective tissue disorders.^{4,5} Furthermore, studies have demonstrated that obtaining extensive routine diagnostic testing without a supporting patient history rarely alters the management and treatment of CSU.²¹

TREATMENT

Both guidelines recommend avoidance of medications such as nonsteroidal anti-inflammatory agents, which might be causing the hives.^{4,5} However, it is important at some point in the

patient's clinical course to do some type of controlled challenge to confirm their causation of CSU because empiric avoidance may hinder future management of conditions that require nonsteroidal anti-inflammatory agents. Both guidelines clearly recommend trying to achieve complete control of the urticaria using the fewest number and safest medications available in order to maximize the patient's quality of life.^{4,5} Figure 2 compares the treatment algorithm of the US guidelines with the international guidelines. Both recommend step 1 therapy with a second-generation H1-antagonist as the first-line treatment of CSU. For step 2 therapy, both guidelines also recommend increasing the dose of the second-generation H1-antagonist to 2 to 4 times the Food and Drug Administration—recommended dose based on safety and efficacy studies as well as clinical experience. Furthermore, both guidelines recommend using these medications on a regular basis to achieve maximum clinical effect rather than as needed.^{4,5} However, the international guideline in contrast to the US guideline recommends against using different second-generation H1-antagonists at the same time because this offers no clinical advantages.⁴ The US and international guidelines also disagree regarding the use of first-generation H1-antagonists.⁵ The US guidelines advocate using these agents at bedtime to minimize their sedation and neurocognitive effects, whereas the international guideline feels that there is enough scientific evidence to support not using them because of their impact on rapid eye movement sleep with prolonged effects

TABLE IV. Alternative treatment options* suggested by the international guideline annotated by the authors of the review

Intervention	Substance (class)	Indication
Widely used		
Antidepressant	Doxepin†	CSU
Diet	Pseudoallergen-free diet‡	CSU
H ₂ -antihistamine	Ranitidine	CSU
Immunosuppressive	Methotrexate Mycophenolate mofetil	CSU ± DPU§ Antibody-associated/autoimmune CSU
Leukotriene receptor antagonist	Montelukast	CSU, DPU
Sulphones	Dapsone Sulfasalazine	CSU ± DPU CSU ± DPU
Infrequently used		
Anabolic steroid	Danazol	Cholinergic urticaria
Anticoagulant	Warfarin	CSU
Antifibrinolytic	Tranexamic acid	CSU with angioedema
Immunomodulator	Intravenous immunoglobulin Plasmapheresis	Antibody-associated/autoimmune CSU Antibody-associated/autoimmune CSU
Miscellaneous	Autologous blood/serum Hydroxychloroquine¶	CSU CSU
Phototherapy	Narrow-band UVB	Symptomatic dermographism
Psychotherapy	Holistic medicine	CSU
Rarely used		
Anticoagulant	Heparin	CSU
Immunosuppressive	Cyclophosphamide Rituximab	Antibody-associated/autoimmune CSU Antibody-associated/autoimmune CSU
Miscellaneous	Anakinra Anti-TNF-α Camostat mesilate# Colchicine Miltefosine Mirtazepine PUVA	DPU CSU ± DPU CSU CSU CSU CSU CSU
Very rarely used		
Immunosuppressive	Tacrolimus	CSU
Miscellaneous	Vitamin D IFN-α	CSU CSU

DPU, Delayed pressure urticaria; PUVA, psoralen and ultraviolet A therapy; UVB, ultraviolet B.

*Treatments that can be considered if treatment according to the recommended algorithm fails or is not possible. Annotations of the authors:

†Has also H₁- and H₂-antihistaminergic properties.

‡Includes a low histamine diet as the pseudoallergen-free diet is also low in histamine; not widely accepted in the United States.

§Treatment can be considered especially if CSU and DPU are coexistent in a patient.

||The international guideline states “autoimmune CSU” only, whereas the US guideline differentiates autoimmune from the presence of antibodies (eg, FcεR1α) that are associated but not cause and effect.

¶More widely used in the United States.

#Not available in the United States.

on motor coordination and alertness on the following day.^{4,5} Furthermore, after publishing the US guideline, a double-blind cross-over study showed that adding a sedating antihistamine at night was not more efficacious.²²

In contrast to the international guideline, the US guideline advocates the use of H₂-antagonists for step 2 therapy because of their safety, marginal efficacy, and potential synergistic effects with H₁-antagonists.^{4,5} They also advocate potentially adding leukotriene-modifying agents (leukotriene receptor antagonist) like montelukast because of the safety and marginal efficacy.⁵ The international guideline has eliminated leukotriene receptor antagonists from their algorithm because of the low level of scientific evidence as previously it was considered step 4 therapy.^{4,23} Furthermore, H₂-antagonists are not included in the treatment algorithm because of a Cochrane review that indicates low level of scientific evidence supporting their use in the

treatment of CU. This review was published after the US guideline was completed.²⁴ Therefore, both the leukotriene receptor antagonist and H₂-antagonists have been relegated to an “Alternative Treatment” table (Table IV) in the updated European Academy of Allergology and Clinical Immunology/WAO guideline.⁴ It is important to emphasize that these medications may still be a therapeutic option for the treatment of CSU but they could not be recommended as first-line agents because of the paucity of scientific evidence supporting their use.⁴ Finally, both guidelines recommend referring patients with CSU to an urticaria specialist if they do not respond well to maximum step 2 therapy.^{4,5}

The updated international guideline recommends the use of omalizumab (Xolair) for patients unresponsive to H₁-antagonists as step 3 therapy based on well-designed robust double-blind placebo-controlled studies demonstrating its efficacy in

CSU.^{25,26} This is in contrast to the US guidelines, which recommend more complex but highly sedating H1-antihistamines such as doxepin or hydroxyzine as step 3 therapy.⁵ As mentioned, these treatments were shifted to the “Alternative Treatment” box in the international guideline because of their sedation and neurocognitive side effects.⁴ However, for step 4 treatments, the US guideline recommends either immunosuppressants (ie, cyclosporine), biologics (ie, omalizumab), or anti-inflammatory agents (ie, hydroxychloroquine, sulfasalazine, dapsone, colchicine...). Although they emphasize that the scientific evidence is strongest for omalizumab, they did not single out omalizumab as the only step 4 treatment as the updated international guidelines have done in the respective step 3.^{4,5} The US guidelines cite at the time of their publications several publications supporting cyclosporine or the anti-inflammatory agents as appropriate treatments for patients unresponsive to H1-antagonists. However, only 1 pivotal trial for omalizumab had been published and omalizumab had not been licensed in the United States for the treatment of CSU until after the US guideline was prepared. The international guideline has placed all the anti-inflammatory agents in the “Alternative Treatment” box because of low scientific evidence supporting their use based on the GRADE approach.⁴ The updated international guidelines do recommend cyclosporine as step 4 therapy for patients unresponsive to omalizumab or who prefer to take oral medications over subcutaneous therapy.⁴

In general, both guidelines recommend not using long courses of oral corticosteroids in the management of CSU. They both suggest a short course of oral corticosteroids in order to control hive exacerbations while attempting to adjust baseline medications intended to prevent recurrences.^{4,5}

The international guideline recommends similar approaches for the treatment of special populations such as children and pregnant or lactating women on the basis of their algorithm.⁴ The US guideline advocates a similar approach but emphasizes the importance of medication safety, disease control, quality of life, and patient preference.⁵

CONTROVERSIAL AREAS BETWEEN US AND INTERNATIONAL GUIDELINES

Probably one of the most contentious disagreements between the US and international guidelines in the past has been the use of a pseudoallergen-free diet to improve symptoms in CU.^{4,5} In the previous version of the international guideline, this approach was recommended after a special vote. Although the hypothesis for therapeutic effects from such a diet is supported by limited scientific studies, there are no well-controlled double-blind placebo-controlled trials supporting its efficacy.²⁷ Furthermore, double-blind provocation studies performed using distillates of foods with preservatives/additives in patients with CSU who seemed to improve on the diet elicited hives in only approximately 20% of these patients.²⁸ For these reasons, the US guideline does not support the use of pseudoallergen-free diets in the management of CU because of the low level of scientific evidence currently available. In the updated version of the international guideline, the lower level of evidence is acknowledged and the pseudoallergen-free diet has been placed in the “Alternative Treatment” box only on the basis of GRADE analysis of this intervention.⁴

The second area of disagreement that still exists is the use of first-generation sedating antihistamines in the treatment of CSU.

The international guidelines strongly advise against the use of first-generation sedating antihistamines on the basis of high level of evidence for adverse events and no studies demonstrating greater efficacy than second-generation antihistamines.^{4,29} Furthermore, first-generation antihistamines have pronounced anticholinergic effects, interactions with alcohol and drugs affecting the central nervous system (ie, analgesics, hypnotics, sedatives, and mood-elevating drugs) in addition to their sedative actions, interference with rapid eye movement sleep, and a negative impact on learning and performance.⁴ However, it should be mentioned that most of these studies have been conducted in healthy volunteers or in patients with conditions other than hives.

CONCLUSIONS

Chronic urticaria is still a mysterious disease to the scientific community. However, it affects millions of individuals and has a significant impact on quality of life and places a substantial economic burden on our health care system. Therefore, it is essential that experts critically analyze the existing literature to provide guidance to clinicians on how best to manage this condition in an efficient, cost-effective manner. Both the US and international guidelines have tried to accomplish this using different methodologies and have generally agreed on most issues pertaining to the management of CSU. The international guideline has developed a very simplistic approach to management largely because the GRADE approach has very strict criteria of what constitutes a high-level scientific study. However, despite relying on GRADE to guide recommendations, it was still necessary for the expert panel assembled by the international guideline's committee to render consensus expert opinions on subjects where the literature was lacking or insufficient. The same was true for the US guidelines because many of the strengths of recommendations made were levels C, D, or E, which are based on weak categories of evidence such as a quasi-experimental study, nonexperimental descriptive or comparative study, or expert committee reports, opinions, or clinical experience, respectively.

As our understanding of the pathomechanisms of CSU improves and new therapies that target specific biologic pathways emerge, these guidelines are bound to change once again. Finally, in the future we expect that further research will allow to better discriminate between subtypes in CSU, giving clues to which alternative medications and novel drugs might be of benefit in individual patients.

However, for now, it is reasonable on the basis of scientific evidence to date, to approach the diagnosis, management, and treatment of CSU using a simplistic algorithm recommended by the updated international guideline. This guideline provides sufficient latitude to adjust or add alternative treatments that, although are not highly supported by scientific studies, have been found to be effective in subsets of patients with CSU. This is especially important for those patients not responsive or incompletely responsive to the GRADE-recommended therapies. However, the US guideline also remains relevant because it provides a compendium of relevant information regarding all aspects of urticaria in which experts should be knowledgeable.

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