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American Academy of Allergy, Asthma and Immunology response to the EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of Urticaria 2017 revision

The most recent EAACI/GA²LEN/EDF/WAO Guideline update on Urticaria was published in the July 2018 issue of ALLERGY.¹ This guideline has been endorsed by 42 national and international

societies including the American Academy of Allergy, Asthma and Immunology (AAAAI). Several aspects of this revised guideline are notable and praiseworthy including the rigorous approach to an

evidence-based appraisal of the literature, the recommendations for limited diagnostic tests in chronic spontaneous urticaria, assessment of disease activity at each patient encounter, and for assessment tools to document disease control. Nevertheless, there are several recommendations that preclude the AAAAI from endorsing all aspects of this guideline. The 10 comments below highlight management recommendations that differ from recommendations in these guidelines; we believe in these instances that our recommendations are most appropriate based on best evidence.

1. The Guideline states: "In contrast, pseudoallergic (non-allergic hypersensitivity reactions) to non-steroidal anti-inflammatory drugs (NSAIDs) or food may be more relevant for chronic spontaneous urticaria (CSU). Diagnosis should be based on history of NSAID intake or a pseudoallergic elimination diet protocol... In some CSU patients, pseudoallergic reactions (non-IgE mediated hypersensitivity reactions) to naturally occurring food ingredients and in some cases food additives have been observed."

Comment 1: Adverse reaction to NSAIDs is based on cyclooxygenase-1 inhibition. There is evidence indicating this is related to exaggerated release of leukotrienes.² We would favor stipulating this as the mechanism for NSAID-exacerbated cutaneous disease, rather than a "pseudoallergic" reaction. Food-provoked urticaria is more relevant for acute urticaria rather than CSU, for which, according to best evidence, foods are a rare cause. Whether a diagnosis of "pseudoallergic" food reaction can be established by a pseudoallergic elimination diet protocol is unclear, as the utility of the latter has not been clearly demonstrated in a placebo-controlled study.³

Chronic urticaria related to food additives may occur; however, adverse reaction to food additives is very rare.⁴

2. The Guideline states: "We recommend against using different H-1 antihistamines at the same time."

Comment 2: While we acknowledge there is a lack of high-quality evidence supporting the therapeutic utility of a combination of 2nd generation H-1 antihistamines, for instance: fexofenadine 180 mg each morning and cetirizine 10 mg at bedtime, there is no evidence for harm and there is evidence for benefit.⁵ Prescribing in this fashion is a common pattern among allergy/immunology physicians in the United States. We do not agree with discouraging this practice.

3. The Guideline states: "The use of omalizumab in pregnancy has been proven to be safe ...".

Comment 3: Safety has not been proven. As an alternative, we would state that at the present time there has been no evidence for maternal or fetal harm.⁶ The decision to administer omalizumab during pregnancy should be approached from an individualized basis, with a careful assessment of the potential for benefit compared with the potential for harm and burden, inviting patients to express their values and preferences and participate in the decision-making process.

4. Table 9 of this Guideline mentions a number of therapeutic interventions for chronic urticaria, including doxepin.

Comment 4: The evidence pertaining to the efficacy of doxepin is of higher quality than a number of the other interventions mentioned in Table 9.⁷ However, recent evidence demonstrates that use of doxepin is associated with an increase in risk for

dementia and Alzheimer's disease in individuals who are 65 years of age and older.⁸ Based on this potential for harm, the decision to prescribe doxepin should be approached with greater caution, and ideally should include an open discussion with patients that encourages them to join the decision-making process.

5. There is no recommendation in the Guideline for prescribing H-2 antihistamines or anti-leukotrienes for treatment of patients with CSU.

Comment 5: The evidence supporting the therapeutic utility of these agents is not high quality. The factors involved in moving from evidence to recommendations via the GRADE approach include an assessment of the balance between desirable and undesirable effects, cost, and patient values and preferences. As H-2 antihistamines and anti-leukotrienes are associated with a very low rate of untoward effects, and moreover these agents are not costly, we believe it is more appropriate to recommend the combination of H-1 and H-2 antihistamines for treatment of chronic urticaria, and administration of montelukast, with a weak recommendation.⁹ A weak recommendation implies that most patients would wish to receive the combination, but many would not.

6. The Guideline includes a strong recommendation to use provocation threshold measurements in management of patients with chronic inducible urticaria (CIU).

Comment 6: While we agree that threshold measurements have been useful tools in clinical research of inducible urticarias, many of these tools are not widely available and have not been studied in large populations, and whether targeting threshold measurements leads to improved outcomes compared to using clinical endpoints alone has not been established. In the United States, even amongst academic centers, very few centers routinely utilize threshold measurements in management of chronic urticaria. Thus, this strong recommendation imposes an unnecessary burden on providers without an appropriate high level of evidence to support this.

7. Alternative treatment options listed by frequency of use.

Comment 7: The guideline includes a table of alternative agents separated by "widely" or "infrequently" used. However, in the United States, "pseudoallergen-free diets" are rarely utilized, whereas hydroxychloroquine is a more frequently utilized alternative agent. Tacrolimus and vitamin D are other agents that are utilized as alternative agents in the United States but are not listed. Autologous blood/serum and psychotherapy are not recommended as alternative treatments in the United States.

8. Strong recommendation to aim for complete symptom control in urticaria.

Comment 8: While complete symptom control is an ideal target, in the majority of patients, this is an unrealistic one and may not be required to meet patients' needs and improve their quality of life. Even with omalizumab 300 mg every 4 weeks, complete control of symptoms that is sustained occurs in <50% of patients.¹⁰

9. Ciclosporin A has high-quality evidence and, aside from omalizumab, is the only other alternative agent recommended.

Comment 9: A previous critical appraisal of the quality of evidence for ciclosporin using the GRADE approach determined this was "low," which led to a "weak" recommendation.⁹ This recommendation appears

to be similar to the consensus in this guideline; however, the representation of ciclosporin as the only other alternative agent in the chronic urticaria treatment algorithm appears to over-emphasize this recommendation. Consideration for the use of other alternative agents after omalizumab failure remains a reasonable treatment strategy.

10. Figure 2 recommends an algorithm for treatment that could escalate to omalizumab in <4 weeks.

Comment 10: The brief time intervals (2–4 weeks or earlier) for steps 1 and 2 stated in this algorithm in some cases could result in a too rapid escalation of therapy to omalizumab. We believe this rapid escalation may result in some patients receiving omalizumab who via a more gradual advancement in H1-antihistamines (with/without H-2 antihistamines combined with anti-leukotriene) could have achieved control of chronic urticaria.

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REFERENCES

1. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO Guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73:1393-1414.
2. Mastalerz L, Setkowicz M, Sanak M, Szczeklik A. Hypersensitivity to aspirin: common eicosanoid alterations in urticaria and asthma. *J Allergy Clin Immunol*. 2004;113:771-775.
3. Di Lorenzo G, Pacor ML, Mansueto P, et al. Food-additive-induced urticaria: a survey of 838 patients with recurrent chronic idiopathic urticaria. *Int Arch Allergy Immunol*. 2005;138:235-242.
4. Rajan JP, Simon RA, Bosso JV. Prevalence of sensitivity to food and drug additives in patients with chronic idiopathic urticaria. *J Allergy Clin Immunol Pract*. 2014;2:168-171.
5. van den Elzen MT, van Os-Medendorp H, van den Brink I, et al. Effectiveness and safety of antihistamines up to fourfold or higher in treatment of chronic spontaneous urticaria. *Clin Transl Allergy*. 2017;7:4.
6. Namazy J, Cabana MD, Scheuerle AE, et al. The Xolair Pregnancy Registry (EXPECT): the safety of omalizumab use during pregnancy. *J Allergy Clin Immunol*. 2015;135:407-412.
7. Greene SL, Reed CE, Schroeter AL. Double-blind crossover study comparing doxepin with diphenhydramine for the treatment of chronic urticaria. *J Am Acad Dermatol*. 1985;12:669-675.
8. Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med*. 2015;175:401-407.
9. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;133:1270-1277.
10. Kaplan A, Ferrer M, Bernstein JA, et al. Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria. *J Allergy Clin Immunol*. 2016;137:474-481.

CORRESPONDENCE

Reply to Wood et al.

As coauthors of the 2017 revision and update of the EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria, we welcome the comments of the AAAAI and provide our responses below.

We very much value scientific discussion of the guideline's recommendations. Already in the planning phase of the revision and update of this international, global guideline, it was agreed among all societies involved that national societies should be encouraged to highlight regional differences in the diagnostic and therapeutic approach to patients with urticaria. Such differences can be based on different legal requirements of the healthcare system, different patient groups, different available resources including the availability of specialists, and cultural aspects.

Whenever worldwide consensus is achieved, not just in medicine, it is clear that the result is the best compromise possible. This is also true for the revision and update of the international urticaria guideline, which benefitted from the contributions and support of the delegates of the AAAAI, during the development of the current recommendations and during the consensus conference. We share the view of our AAAAI colleagues that a clear aim of our international guideline is to better harmonize the approaches in urticaria globally.¹

Our responses to the 10 comments of our AAAAI colleagues on the 2017 revision and update of the international urticaria guideline² are as follows:

Comment #1: We agree that the term “pseudoallergy”, although used and understood worldwide, is not ideal, but suggested alternatives like non-IgE mediated hypersensitivity reaction are unfortunately not very practical in talking with the patient. Regarding the mechanisms, we agree that they are currently not well understood. More research is needed and being undertaken.

Comment #2: It is well known that it is common practice to combine different antihistamines, but as the authors themselves state there is little evidence in support of this practice. The little evidence that does exist points to a benefit of up dosing one antihistamine vs combining several. This is supported by general pharmacological considerations including the need to minimize the risk of adverse drug interactions. This also applies to the treatment of skin and allergic diseases, where we do not, in daily practice, combine different corticosteroids or leukotriene antagonists. An evidence-based guideline cannot recommend to combine antihistamines, when there is no evidence in support of this and some, albeit weak, evidence against it.³

Comment #3: You mention that the use of omalizumab in pregnancy has not been *proven* to be safe. We agree that the word

“proven” should always be used with care, especially when informing the patient about potential adverse events of the treatment recommended. With the use of any medication, as of yet unobserved harm cannot be ruled out with certainty.

Comment #4: You are warning against the use of doxepin. We very much value this comment, and we are in complete agreement with our AAAAI colleagues on this.

Comment #5: Both, H₂ antagonists and leukotriene antagonists, are listed as fifth-line treatment options in the current version of the international guideline, to be considered if antihistamine treatment at standard and higher than standard dose, omalizumab and/or ciclosporin have failed or are not available. The reason both drugs were removed from the treatment algorithm is the lack of high-level evidence in support of their efficacy.⁴ The guideline is transparent on this and says that, based on the level of evidence, “we cannot make a recommendation” for the use of these agents.

Comment #6: While it is recommended to assess trigger threshold levels in patients with chronic inducible urticaria, there is no recommendation on how to do this specifically. Knowledge of threshold levels helps patients to avoid relevant trigger exposure and can help physicians to individualize and optimize treatment.

Comment #7: The frequency of use of different therapies by nature will be different in different areas of the world. We provide a consensus of the worldwide group of authors and recognize that this global approach may differ from the AAAAI approach.

Comment #8: To aim for complete symptom control in urticaria as recommended by the current and previous version of the international urticaria guideline implements the expectations of the Constitution of the WHO.⁵ It is agreed that this may not always be possible, which is why the recommendation says to “aim at” this.

Comment #9: While it is desirable to have more fourth-line treatment options, in addition to ciclosporin no other treatment is currently supported by similar level evidence.⁶ Hopefully, future trials will change this.

Comment #10: You criticized that the brief time intervals (2–4 weeks or earlier) for steps 1 and 2 stated in the algorithm in Figure 2 in the guideline¹ in some cases could result in a too rapid escalation of therapy to omalizumab. Pharmacologically, antihistamines show efficacy within a few days and reach steady state efficacy within a few weeks. In fact, most antihistamines reach maximum activity in approximately four half-lives. Antihistamine treatment for longer than 2 weeks does not increase efficacy in urticaria.⁷

In summary, many of the AAAAI's comments are important and help to further develop the international urticaria guideline. Some

can only be addressed conclusively once the results of ongoing and future studies are available. We, therefore, urge the AAAAI and our AAAAI colleagues to support these studies. GA²LEN has, for this purpose, created a network of urticaria centers of reference and excellence (UCAREs).⁸ We count on the support and contributions of our AAAAI colleagues and the AAAAI in the development of the next revision and update of the international urticaria guideline.

CONFLICTS OF INTEREST

The conflicts of interest have been stated in detail in the guidelines methods report.⁴

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REFERENCES

1. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73:1393-1414.
2. Wood RA, Fasano MB, Khan D, et al. AAAAI response to EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria 2017 revision. *Allergy*. <https://doi.org/10.1111/all.13636>. [Epub ahead of print].
3. Schulz S, Metz M, Siepmann D, Luger TA, Maurer M, Stander S. Antipruritic efficacy of a high-dosage antihistamine therapy. Results of a retrospectively analysed case series. *Hautarzt*. 2009;60:564-568.
4. Dressler C, Rosumeck S, Werner RN, et al. Executive summary of the methods report for 'The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. The 2017 revision and update'. *Allergy*. 2018;73:1145-1146.
5. Constitution of the WHO. <http://www.who.int/about/mission/en/>. Accessed 22 July 2018.
6. Kulthanan K, Chaweekulrat P, Komoltri C, et al. Cyclosporine for chronic spontaneous urticaria: a meta-analysis and systematic review. *J Allergy Clin Immunol Pract*. 2018;6:586-599.
7. Magerl M, Pisarevskaja D, Staubach P, Martus P, Church MK, Maurer M. Critical temperature threshold measurement for cold urticaria: a randomized controlled trial of H₁-antihistamine dose escalation. *Br J Dermatol*. 2012;166:1095-1099.
8. Maurer M, Metz M, Bindslev-Jensen C, et al. Definition, aims, and implementation of GA²LEN urticaria centers of reference and excellence. *Allergy*. 2016;71:1210-1218.