



Chronic Urticaria: Comparisons of US, European, and Asian Guidelines

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Abstract

Purpose of Review Chronic urticaria is a common dermatological condition that has significant impact on quality of life. Multiple international societies have published guidelines, and although these guidelines generally agree on the definition of urticaria, as well as approach to diagnosis and management, there have been notable differences to date. These differences have been reconciled by the recent publication of the 2017 revision and update published by the EAACI/GA2LEN/EDF/WAO.

Recent Findings The 2017 revision and update to the guidelines for chronic urticaria are the most comprehensive consensus document to date, and reconcile previously existing differences between the US, European, and Asian guidelines.

Summary The purpose of our review is to present basic background on urticaria and discuss classification, diagnosis, and most importantly, management. We present differences from previous US, European, and Asian guidelines and reconcile the previous differences by summarizing the 2017 revision and update published by the EAACI/GA2LEN/EDF/WAO.

Keywords Urticaria · Hives · Angioedema · Urticaria guidelines · Diagnosis of urticaria · Management of urticaria · Urticaria activity score · Urticaria treatment algorithm · 2017 revision and update

Introduction

Urticaria is a dermatologic disorder mediated by mast cell degranulation, leading to erythematous, raised, blanching wheals. Lesions are typically non-painful but pruritic and resolve within 24 h, leaving no residual bruising, scarring, or changes in skin pigmentation. Approximately 40% of cases are associated with angioedema, which represents a continuum of disease with a similar pathophysiology but involves the deeper layers of the sub-dermis [1]. Angioedema can also occur in the absence of urticaria, and this may represent a

different clinical entity. Angioedema without urticaria warrants a detailed evaluation aimed at investigating the bradykinin pathway. Acute urticaria lasts less than 6 weeks, whereas chronic urticaria lasts more than 6 weeks. Acute episodes are more likely to have an identifiable cause, such as foods, medications, or viral infection, particularly in children. The etiology of chronic urticaria is a far more complex process and often difficult to ascertain.

The prevalence of urticaria and angioedema varies depending on geography and the population being studied. Up to 20% of individuals will experience acute urticaria at some point during their lifetime, and 0.1% will develop chronic symptoms [2, 3]. The lifetime prevalence of chronic urticaria is approximately 1.8% [4]. Chronic urticaria affects more women than men, 60% versus 40%, respectively. As a rule of thumb, 50% of individuals with chronic urticaria experience spontaneous resolution within 1 year, and 80% experience resolution by 5 years. Predictors of protracted duration include the presence of physical triggers, angioedema, and the presence of autoantibodies [5, 6]. Although there are recent reports showing an increased rate of hospital admission for cases of urticaria, particularly associated with angioedema [7], the major impact of chronic urticaria remains on a significantly decreased quality of life [8].

This article is part of the Topical Collection on *Allergic Skin Diseases*

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Worldwide Societies

Since chronic urticaria is a common disorder with significant impact on quality of life and health care utilization, multiple international societies have weighed in with guidelines on diagnosis and management. The guidelines are uniformly based on scientific research, and where there is insufficient evidence to draw a conclusion, the recommendations are guided by expert opinion. This review will briefly describe the various guidelines, highlighting not only essential similarities, but also important differences. Based on the grade of the evidence, this review will attempt to reconcile any differences by defining a universal approach.

In the USA, the American Academy of Allergy, Asthma, and Immunology (AAAAI) and American College of Allergy, Asthma, and Immunology (ACAAI) Joint Task Force (JTF) is the consensus group contributing to guidelines on chronic urticaria [9•]. The other major consensus group includes the European Academy of Allergy and Clinical Immunology (EAACI) and World Allergy Organization (WAO) [10•]. It should be noted that the WAO is a consortium of 97 regional and national allergy and clinical immunology societies. This group recently published updated guidelines, that have also been endorsed by the AAAAI and ACAAI, along with Asian societies as well [11••]. Forty-four experts from 25 countries contributed to this effort. As a result of the Asian-Australian Regional Conference of Dermatology, there have also been specific guidelines published from Asia by the Asian Academy of Dermatology and Venereology (AADV) Study Group in collaboration with the League of Asian Dermatological Societies in 2010 [12•]. The Japanese Dermatological Association (JDA) has also published its own set of guidelines [13]. The JDA guidelines have largely not been recognized outside of Japan due to the language barrier. To date, the guidelines by Zuberbier et al. published in *Allergy* 2018 are the most comprehensive document on consensus recommendations on the diagnosis and management of chronic urticaria. Table 1 summarizes the major guidelines.

Classification and Assessment

Prior to the most recent guidelines, there were subtle differences in nomenclature between the European and American approaches. The JTF practice parameter referred to chronic urticaria as occurring “continuously” or “intermittently” for at least 6 weeks. In individuals with chronic urticaria and presence of autoantibodies (IgG against FcεR1a, thyroid antibodies (thyroglobulin, thyroid peroxidase), RF, ANA), the JTF suggested calling these cases “autoantibody-associated chronic urticaria.” The JTF guidelines go into significant detail regarding the diagnostic testing and specific features of

physical urticarias, including dermatographism, solar, aquagenic, vibratory, cholinergic, cold, and delayed pressure angioedema. The European and world guidelines focus on “spontaneous” urticaria which is idiopathic in nature, versus chronic “inducible” urticaria (CInU), such as physical urticaria. This terminology has been agreed upon by > 90% consensus, as per the recent 2017 revision and update by Zuberbier et al. All guidelines, regardless of continent, include angioedema in the definition of urticaria. Guidelines also universally emphasize the importance of differentiating urticaria from anaphylaxis. All documents also emphasize the importance of chronic urticaria being a diagnosis of exclusion, after appropriate evaluation of other conditions. Although most guidelines encourage practitioners to use tools to objectify symptoms of urticaria, the EAACI/WAO has previously specifically recommended using the urticaria activity score (UAS7) in clinical practice (Table 2) [14]. Additional tools include the angioedema activity score (AAS) [15] and urticaria control test (UCT) [16, 17].

Diagnosis

Most guidelines to date, including the JTF and EAACI/WAO documents, along with Asian guidelines, agree that the diagnostic evaluation in chronic urticaria should be based on the history and physical examination. Limited laboratory testing with a complete blood count with differential (CBC), erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) is considered appropriate. The JTF has also included liver function tests (LFTs) and thyroid stimulating hormone (TSH) as appropriate evaluation in chronic urticaria. Neither group recommends routine evaluation for celiac disease, or infectious conditions such as *Helicobacter pylori* or hepatitis. Additionally, neither group recommends checking for autoantibodies, or completing routine testing for IgE-mediated allergy to foods or aeroallergens. Elimination of foods or medications can be considered to evaluate the possibility of an underlying trigger. The 2017 guidelines by Zuberbier et al. specifically recommend considering NSAIDs as a trigger for chronic urticaria, a well-known exacerbating factor of ongoing urticaria [18]. Despite a consensus on limiting a routine diagnostic evaluation, the JTF acknowledges that it may serve to alleviate patient stress and anxiety. The EAACI/WAO suggests to consider testing, such as checking for autoantibodies, on a case by case basis. When considering laboratory testing in chronic urticaria, it is important to be aware that testing is typically of low utility, as shown by Tarbox et al. [19]. Lastly, all guidelines agree that unless there is concern for vasculitis, skin biopsy is rarely needed.

Although IgE mediated food allergy is felt to be a rare cause of chronic urticaria, the role of food elimination diets remains controversial in the management of this condition.

Table 1 Comparison between urticaria guidelines

	AADV (Asian) 2010 Guidelines	EAACI/EDF/WAO 2013 Guidelines	JTFPP 2014 Guidelines	2017 Revision and update
Nomenclature	Chronic spontaneous urticaria Physical urticaria	Chronic spontaneous urticaria Chronic inducible urticaria	Chronic urticaria Physical urticaria Autoantibody associated chronic urticaria	Chronic spontaneous urticaria Chronic inducible urticaria
Recommended lab evaluation	CBC, ESR, CRP	CBC, ESR, CRP	CBC, ESR, CRP, LFTs, TSH	CBC, ESR, CRP
Extended lab evaluation (<i>Helicobacter pylori</i> , autoantibodies)	Recommended on case by case basis	Recommended on case by case basis	Not recommended	Recommended on case by case basis
Pseudoallergen-free diet	Recommended on case by case basis	Recommended on case by case basis	Not recommended	Recommended on case by case basis
First-generation antihistamines	Not recommended	Not recommended	Recommended second and third steps	Not recommended
Anti-H2 antihistamines	Recommended fourth step	Not recommended	Recommended second step	Not recommended
LTRA	Recommended third step 3–7 days	Recommended third step Up to 10 days	Recommended second step 1–3 weeks	Not recommended Up to 10 days
Systemic corticosteroids for exacerbations				
Additional therapies	Omalizumab or Cyclosporine or Dapsone	Omalizumab or Cyclosporine	Omalizumab or Cyclosporine	Omalizumab preferred over Cyclosporine

Due to low levels of scientific evidence through well-designed double-blind randomized controlled studies, the JTF does not support the use of pseudoallergen-free diets. The EAACI/WAO, on the other hand, is amenable to a trial of pseudoallergen-free diet, which avoids certain naturally occurring food ingredients and additives, in a subset of cooperative and motivated patients. If embarking on this type of elimination diet, it must be followed for two to three consecutive weeks in hopes of observing beneficial effects. The EAACI/WAO acknowledges that although outcomes are widely variable, and depend on a host of individual factors, including dietary habits and various other regional differences, there are favorable reports of this strategy improving outcomes in patients with chronic urticaria [20].

Management

The goal of therapy is to achieve complete symptomatic relief while using the least amount of medications with the least adverse effects. Although the principles of therapy have been similar between all guidelines and governing bodies, prior to the updated 2017 guidelines, there were subtle differences in the specific approach to recommended management. All guidelines agree upon avoiding identifiable triggers. This includes not only physical triggers, but also medications, such as NSAIDs, which can exacerbate lesions in up to 1/3 of patients [21].

Due to strong evidence, all guidelines agree with starting with approved doses of non-sedating, second-generation antihistamines. Sanchez-Borges et al. outline relative efficacy of specific agents in their WAO position paper published in 2012 [22•]. Cetirizine is superior to fexofenadine [23], while levocetirizine is superior to desloratadine [24] but has similar efficacy to bilastine [25]. In vivo studies have shown cetirizine and levocetirizine to be superior in suppressing histamine-induced wheal and flare as compared to other agents [26]. If symptoms remain on typical doses, all guidelines suggest increasing the dose of the second-generation antihistamine up to fourfold, and there is primary evidence to support this approach [27, 28]. In the JTF guidelines, this dose escalation can be considered in step 2 of therapy. Additional considerations in step 2 include adding another second-generation antihistamine, adding an H2 antagonist, adding a leukotriene receptor antagonist, or adding a first-generation antihistamine at night. Citing a poor body of evidence, the EAACI/WAO guidelines do not endorse using a leukotriene receptor antagonist, H2 antagonist, or the combination of first-generation and second-generation antihistamines. Very importantly, although first-generation antihistamines also have been shown to be uniformly efficacious in the management of chronic urticaria, their efficacy is similar to second-generation antihistamine [29], yet they are associated with significant

Table 2 Urticaria activity score 7—validated, objective assessment of disease activity

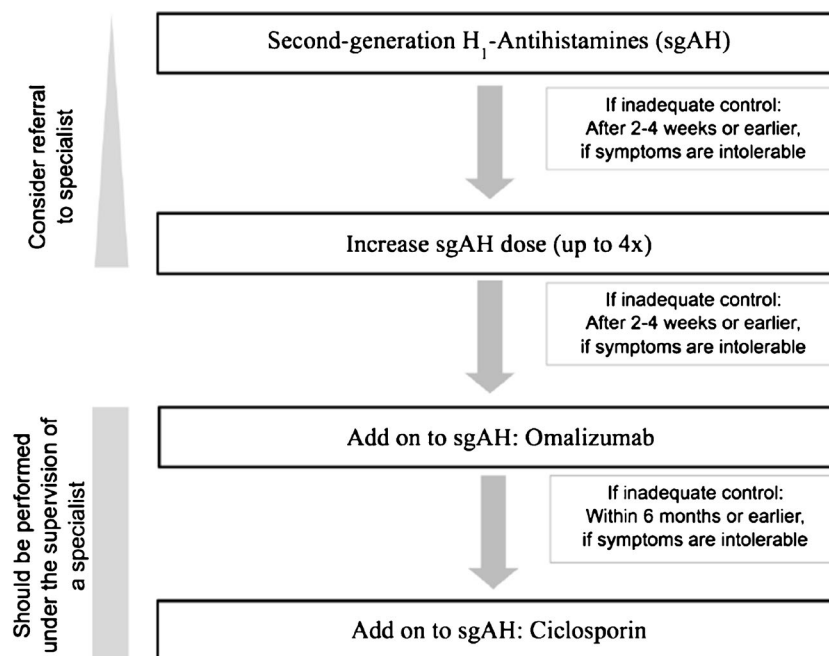
Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 h)	Mild (present but not troublesome)
2	Moderate (20–50 wheals/24 h)	Moderate (troublesome but does not interfere with activity and/or sleep)
3	Severe (> 50 wheals/24 h)	Severe (troublesome and interferes with activity and/or sleep)
UAS7 = sum of score 0–6 daily for 7 days		

Mlynec A et al. *Allergy* 2008; 63: 777–80

somnolence and additional anticholinergic effects [30]. It should be noted that for some individuals, somnolence with first-generation antihistamines can improve after 3–5 days of therapy. Similar to European guidelines, Asian guidelines also discourage the use of leukotriene receptor antagonists or H2 antagonists unless other therapies are failing.

Prior to the 2017 guidelines by Zuberbier et al., there was a difference in therapeutic approach between the JTF guidelines and the EAACI/WAO and Asian guidelines regarding the role of leukotriene receptor antagonists and H2 blockers. The JTF practice parameters recommended the addition of leukotriene receptor antagonists or H2 blockers as step 2 of therapy in patients failing monotherapy with second-generation antihistamines. In regard to leukotriene receptor antagonists, relatively small, randomized, double-blinded studies have suggested potential benefit in addition to second-generation antihistamines, but this benefit may be limited to a small subset of patients with urticaria [31–34]. The EAACI/WAO guidelines specifically state that the evidence for using leukotriene receptor antagonists in urticaria is inconsistent, and a systemic

review of the literature shows modest if any benefit [35]. With that being said, the EAACI/WAO document also notes that despite the low-grade evidence, given the excellent safety profile of leukotriene receptor antagonists, they may be tried in patients with urticaria who are unresponsive to antihistamines. The discrepancy on leukotriene receptor antagonists has been reconciled in the latest 2017 guidelines by Zuberbier et al., which now has a consensus to no longer use these agents in the stepwise treatment of chronic urticaria. Similarly to leukotriene receptor antagonists, the JTF practice parameters included H2 blockers as an option in step 2 of therapy, whereas the EAACI/WAO did not recommend use of these agents due to low-grade evidence. Favorable studies of H2 blockers in combination with H1 antihistamines typically used cimetidine [36–38], with similar results lacking for ranitidine [39, 40]. As stated in the WAO Position Paper by Sanchez-Borges et al., the effectiveness of cimetidine is thought to be due to its ability to inhibit cytochrome p450 isoenzymes, which are involved in the metabolism of first-generation antihistamines, like hydroxyzine and cetirizine.

**Fig. 1** Chronic urticaria treatment algorithm. Zuberbier T et al. *Allergy* 2018. Epub ahead of print

The addition of cimetidine, therefore, theoretically increases plasma concentrations of these medications, thereby improving control of urticarial lesions [41, 42]. The quality of evidence is therefore low, and H2 antagonists are no longer included in the stepwise treatment of chronic urticaria in the most recent 2017 worldwide guidelines by Zuberbier et al.

All guidelines agree that additional therapy beyond antihistamines should be reserved for the last step in therapy of chronic urticaria. Although numerous immune-modulating agents have been reported to be effective in urticaria [43•] and are covered in the EAACI/WAO document, the JTF practice parameters specifically favors the use of cyclosporine or omalizumab as step 4 of therapy, because these two agents are felt to have the best supporting evidence [44, 45•, 46–48, 49•]. Although the risk of adverse side effects with immune-modulating agents must be weighed against the benefit, all guidelines favor using these agents over prolonged use of systemic steroids, which are universally felt to be efficacious but unsafe over time. The updated 2017 guidelines by Zuberbier et al. specifically favor the use of omalizumab over cyclosporine due to the higher incidence of adverse effects seen with cyclosporine (Fig. 1). Nevertheless, cyclosporine remains preferable to the long-term use of systemic steroids, but should be reserved for patients who have failed both increased doses of antihistamines as well as omalizumab.

Special Considerations

The EAACI/WAO guidelines address special situations whereas the JTF practice parameters and Asian guidelines do not. Infections are noted to potentially play a more important role in pediatric urticaria as compared to urticaria in the adult population. Medical therapy in children should almost solely focus on non-sedating second-generation antihistamines, and not first-generation antihistamines, due to their potential of sedation. A similar approach should be taken during pregnancy and lactation. The EAACI/WAO is reassuring about the use of systemic steroids during breast feeding, since minimal amounts of steroid have been found in breast milk [50, 51]. None of the documents discuss the natural history of urticaria in great detail but do note a favorable prognosis in which most patients experience spontaneous resolution of the condition.

Conclusion

Urticaria is a common skin condition that has significant adverse impact on quality of life. The underlying etiology is complex and difficult to identify. Urticaria is a typically a clinical diagnosis, with symptomatic therapy focusing on the

use of antihistamines. Numerous worldwide societies have published guidelines on the management of urticaria, and although these documents are in agreement on most points regarding the definition, etiology, diagnosis, and management, subtle differences have existed. A true worldwide agreement on the diagnosis and management was recently reached and published in 2018 and should serve as the consensus document on the diagnosis and management of chronic, spontaneous urticaria.

Compliance with Ethics Guidelines

Conflict of Interest S. Shahzad Mustafa declared that he is on the speaker's bureau for Genentech.

Mario Sánchez-Borges declared that no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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