

# Urticaria Guidelines: Consensus and Controversies in the European and American Guidelines

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**Abstract** Urticaria can present acutely and be self-limiting or become chronic and persist for weeks, months, or years. In either case, the condition may have a significant impact on the patient's quality of life. Two major consensus groups, the EAACI/WAO and the AAAAI/ACAAI Joint Task Force, have written guidelines on the diagnosis and management of urticaria. While both agree on most points regarding the definition, general evaluation, and treatment, there are some differences which exist. The guidelines, which are written to assist both primary practitioners and specialists in managing their patients with urticaria, have been developed based on scientific evidence, and when insufficient evidence is available, then recommendations are based on expert consensus opinion. The majority of the differences between the two guidelines pertain to recommendations based on expert opinion because of weak scientific evidence. Within this

document, we compare the recommendations of these two groups, highlighting the key similarities and differences.

**Keywords** Urticaria · Hives · Angioedema · Guidelines for urticaria · Diagnosis of urticaria · Management of urticaria

## Introduction

Urticaria is a heterogeneous skin disorder that may be acute or chronic, intermittent or persistent, and may occur alone or in association with other related conditions such as angioedema and, in its most severe form, as part of anaphylaxis. Two major groups have recently published practice parameters for the evaluation and management of acute and chronic urticaria which involved collaboration of experts from a variety of medical specialties including internal medicine, pediatrics, allergy/immunology, and dermatology [1•, 2•]. The AAAAI/ACAAI Joint Task Force (JTF) practice parameters on urticaria were most recently updated in 2014. Each recommendation is made based on the level of evidence in the literature. Each level of evidence is ranked a category of evidence ranging from I to IV. Grading of Recommendations Assessment, Development and Evaluation approach for critical appraisal of evidence was used for certain recommendations such as the therapeutic utility of cyclosporine for refractory chronic urticaria/angioedema. In 2008, a separate group of experts met at the 3rd International Consensus Meeting on Urticaria which included the Dermatology Section of the European Academy of Allergy and Clinical Immunology (EAACI), the EU-funded network of excellence, the Global Allergy and Asthma European Network (GA<sup>2</sup>LEN), the European Dermatology Forum (EDF), and the World Allergy Organization (WAO) [3]. Their practice parameter 2013 revision and update as well as an accompanying methods report were recently published

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[1•, 4]. Not surprisingly, these two documents which independently review the pathophysiology and treatment of urticaria have many common conclusions and recommendations but also highlight some significant differences in the evaluation and management of urticaria. The following article addresses the similarities and differences that exist between these two documents.

## Definition, Classification, and QOL Effect

Urticaria is commonly defined as the sudden appearance of wheals with central swelling and surrounding erythema which are typically pruritic and resolve within about 24 h without scarring, although some lesions may last up to 48 h before resolving [1•, 2•, 5]. Lesions lasting longer than 24–48 h, those which leave hyperpigmentation, or lesions which burn may be vasculitic rather than urticarial, and skin biopsy may be necessary to differentiate between these two disorders.

Both the EAACI/WAO and JTF include angioedema in the definition of urticaria, which suggests that urticaria and angioedema may have a similar pathophysiology and may also exist in the same spectrum of disease. Angioedema is a less well-circumscribed area of edema which occurs in the deeper dermis compared to urticaria. Nevertheless, in both urticaria and angioedema, the wheal or swelling is likely the result of the release of histamine and other mediators from mast cells and basophils, and erythema the result of vasodilation [5]. It may be either histaminergic or non-histaminergic, the latter of which could be bradykinin mediated or secondary to other poorly elucidated pathways (idiopathic). Angioedema can occur concurrently with urticaria in up to 40 % of cases but may occur alone in up to 10–20 % of cases. Urticaria is generally a self-limiting innocuous condition but can present with systemic symptoms, associated with anaphylaxis where the patient may experience gastrointestinal or respiratory symptoms, or angioedema [2•]. Therefore, both parameters emphasize the importance of differentiating urticaria from anaphylaxis as the latter may require emergency treatment including administration of an epinephrine autoinjector.

It is important to understand the various types of urticaria which are classified based on acuity and etiology. Acute urticaria, by definition, is the presence of urticaria for less than 6 weeks. Acute or chronic urticaria may occur as a result of mast cell and basophil release of bioactive mediators such as histamine and leukotrienes, after activation of either the innate or adaptive immune system. Therefore, urticaria can result from activation by specific IgE, by IgM, or by IgG activation of the classical complement pathway, or other mediators that can directly activate mast cells and/or basophils (neuropeptides, opiates) or lead to cellular production of newly formed mediators (i.e., ASA, NSAIDs). While allergic triggers are often considered in cases of acute urticaria, there are many

other known and proposed mechanisms by which acute urticaria may occur. In fact, infection may be the most common cause in pediatric cases, with medications and foods combined causing only about 8 % of cases [1•, 2•].

Urticaria is considered chronic when it persists for greater than 6 weeks. Although many definitions state that in chronic urticaria symptoms should be present 3 days a week or more, neither the JTF practice parameter nor the EAACI/WAO guideline specifies a frequency required for a diagnosis of chronic urticaria [6–9]. Both groups agree that chronic urticaria can be divided into two major subtypes. However, there are differences in terminology related to describing hives. The EAACI/WAO document uses the terms “spontaneous” and “inducible,” whereas the JTF practice parameter uses the terms “continuous” and “intermittent” to describe the variable nature of hives. Inducible hives are physical urticarias which occur as a result of exposure to specific triggers (i.e., cold, pressure, exercise, UV light, heat, vibration, water) and can be controlled by avoiding these triggers, whereas spontaneous urticaria, whether acute or chronic, occurs without known provocation [1•, 2•]. In children, physical factors may cause or contribute to the majority of chronic urticaria cases presenting to clinicians [5, 10, 11]. The JTF practice parameters point out that physical urticaria may occur alone or in conjunction with chronic urticaria and go into further detail than the EAACI/WAO parameters on the difference in appearances of urticaria as well as diagnostic techniques [1•, 2•]. However, both documents are careful to emphasize that the term chronic idiopathic urticaria is a diagnosis by exclusion and should not be used to immediately characterize any patient presenting with chronic urticaria.

Acute and chronic urticaria affect up to 20 and 5 % of the general population, respectively. Chronic urticaria can have a significant impact on quality of life (QoL) [2•, 12]. The EAACI/WAO guidelines specifically address quality of life in acute and chronic urticaria. The urticaria activity score (UAS), a validated scoring system commonly used in the literature and recommended by the EAACI/WAO, considers severity of pruritus and wheals to create a score ranging from 0 to 6 [13–15]. This score can be summed over 24 h for 7 consecutive days to create the UAS7 for that patient, with a possible total score of 0–42 (Table 1). The EAACI suggests that this score can be used in clinical practice to determine disease activity and response to treatment for chronic urticaria. This score was recently used as a primary or secondary endpoint in recent clinical trials assessing omalizumab for the treatment of chronic urticaria (CU) unresponsive to H1 antihistamines [18]. The CU-Q2oL is another instrument, validated in multiple languages, which is available for assessing the severity of chronic urticaria quality of life impairment [1•, 15, 16, 19, 20]. The 2014 updated JTF practice parameter does not specifically address quality of life or assessment of impairment in quality of life in urticaria as this instrument had not

**Table 1** Assessment of disease activity in urticaria patients (UAS7 [4, 17])

| 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 (Sum scores over 7 days for UAS7)

been adequately validated. However, it does recommend obtaining objective measurements that quantify the severity of itch (itch severity score) and the percentage of the body covered in hives at any given time (visual analog scale) in order to assess severity of hives and response to treatment.

### Evaluation for Chronic Urticaria

For those with chronic urticaria, since the underlying cause is seldom found, extensive laboratory testing is not recommended. Instead, the evaluation should focus on a directed history and physical, similar to what is recommended for acute urticaria. Both the JTF practice parameter and the EAACI/WAO practice parameter agree that a limited routine workup is appropriate in chronic urticaria including a CBC with differential, ESR or CRP, and elimination of the possibility of underlying causes such as medications or foods. These tests might identify a chronic condition which could be treated and therefore lead to the resolution of urticaria, if there is an association. The JTF practice parameter includes liver function enzymes and TSH in their limited routine workup, although neither group supports routine testing for thyroid antibodies as there is not sufficient evidence to support the utility of this test in managing CU. Both the JTF and EAACI/WAO provide some latitude for additional testing to identify other underlying causes if there is clinical suspicion based on a thorough history and physical examination. However, routine assessment for *Helicobacter pylori*, celiac disease, and chronic infections like hepatitis B and C is not recommended. In general, neither document recommends routine testing for IgE-mediated responses to aeroallergens for the evaluation of chronic urticaria.

Chronic urticaria often has no clear etiology, and this case is therefore termed chronic idiopathic urticaria. However, more recently, it has been proposed that about 50–60 % of cases of those with chronic idiopathic urticaria have an underlying autoimmune etiology, which has been referred to as chronic autoimmune urticaria. Although there may be an autoimmune component to some cases of CU, it is not known whether there is any true etiologic connection between specific antibodies and autoimmune disorders and CU [6].

Furthermore, the therapeutic and prognostic values are not known. Thirty to 50 % of chronic urticaria patients produce specific IgG antibodies against the FcεRIα subunit component of the high-affinity IgE receptor, and 5 to 10 % produce IgG antibodies against IgE itself [2•]. Many CU patients produce other autoantibodies such as thyroid antibodies (i.e., antithyroglobulin antibodies and thyroid peroxidase antibodies), rheumatoid factor, and ANA. Since the functional significance of these antibodies related to treatment outcomes is still unclear, the JTF practice parameter has recommended that the term “autoantibody associated chronic urticaria” replace chronic autoimmune urticaria [2•, 8, 9]. In addition, testing for SLE, rheumatoid arthritis, autoimmune thyroid disease, and the IgE receptor autoantibody as well as treatment of these diseases with a focus on or expectation to resolve the chronic urticaria is not recommended [1•, 2•]. The determination of autoimmunity in autoantibody-associated chronic urticaria has been made by either an autologous serum or plasma skin test or in vitro using basophil histamine release assays [9, 21]. Due to lack of sufficient evidence to support its utility in managing urticaria, the JTF practice parameter does not support the use of these assays in evaluating urticaria while the EAACI/WAO practice parameter acknowledges the controversial nature of this testing and recommends its use as part of an extended panel on a case-by-case basis [1•, 2•].

The JTF practice parameter consensus is that extensive testing does not provide sufficient information that alters the management of the CU patient and therefore is not routinely recommended. The JTF practice parameter does indicate that select testing in some circumstances may be appropriate to reassure a patient and alleviate their anxiety and concerns regarding a potential cause of their hives. Whereas the JTF practice parameter does not advocate in vitro for FcεRI1 alpha subunit antibodies over in vivo testing, the EAACI/WAO supports the basophil histamine release assay over autologous serum skin testing. This position paper and a separate position paper from the EAACI/WAO on the ASST do address the poor standardization of this test although, given the high negative predictive value, they endorse it as a useful tool to rule out the presence of circulating autoantibodies [1•, 22]. Both parameters agree that biopsy is rarely indicated, and if performed, the histopathologic finding is predominantly a

lymphocytic infiltrate [1•, 2•]. A separate GA<sup>2</sup>LEN task force report also addresses the potential role of stress in chronic urticaria which is not adequately addressed by the JTF practice parameter guideline [23]. Further research on the effect of stress on urticaria and subsequent impact of urticaria on quality of life is needed.

## Natural History

There are few long-term studies which have evaluated the long-term remission of patients with chronic urticaria. These outcomes are only briefly discussed by both documents. However, some studies suggest that in both adults and children, there is a 30–50 % remission rate in CU within the first 3 years after onset of symptoms, whether it is considered idiopathic or autoimmune [24, 25]. Longer courses of urticaria have been reported in patients with a physical urticaria component [26].

## Treatment

The cornerstone of treatment for urticaria, as in most allergic conditions, is avoidance of any known trigger. However, often and especially in chronic cases as previously discussed, no clear etiology or trigger is usually identified. If avoidance is not possible, then the next widely recommended and utilized treatment step for both acute and chronic urticaria is the use of H1 antihistamines. While most patients respond well to this class of antihistamines, many may require higher doses of H1 antihistamines alone or in combination with other classes of medications including leukotriene receptor antagonists, H2 antihistamines, or first-generation H1 antihistamines dosed at bedtime to avoid or lessen the sedating side effects of these agents. For refractory cases, short courses of oral corticosteroids are often required.

In the practice parameter step care approach, treatment is initiated based on the patient's urticaria severity, typically with FDA-approved doses of second-generation antihistamines. Overall, second-generation antihistamines such as cetirizine, levocetirizine, fexofenadine, desloratadine, and loratadine are the preferred step 1 approach. If this is not sufficient, one or more of the following can be done for further control: the dose of the second-generation antihistamine can be increased to two to four times the recommended dose, another second-generation antihistamine can be added, a leukotriene-modifying agent can be added, an H2 antihistamine can be added, and/or a first-generation H1 antihistamine can be added at bedtime.

However, the second-generation H1 antihistamines when administered two to four times the recommended FDA-approved dose as recommended in the step 2 care approach in the JTF practice parameter can also cause

sedative side effects in a subset of susceptible individuals [2•]. For those patients who suffer from sedative effects of the generally non-sedating H1 antihistamines, fexofenadine, levocetirizine, and desloratadine can be used [27, 28•]. Some studies have found that the combination of antileukotrienes with antihistamines may be superior to antihistamine monotherapy [29–31]. Other studies have shown that antileukotrienes given in combination with H1 antihistamines especially in patients with a positive autologous skin test may significantly reduce symptom severity as measured by symptom scores [32]. The third step recommended is advancement of the first-generation H1 antihistamines or combination agents (doxepin or hydroxyzine) if tolerated. If this is not tolerated due to excessive sedation or if it is not effective, then CU would be considered refractory and advancement to the fourth and final step is recommended which would include anti-inflammatories (hydroxychloroquine, dapsone, sulfasalazine, colchicine), immunosuppressants (cyclosporine, mycophenolate, tacrolimus, methotrexate), or biologics, notably omalizumab (Xolair™) [2•].

The EAACI/WAO step approach is very similar to that outlined by the JTF although there are some notable differences (Table 2). First-line treatment advocates use of second-generation antihistamines, favoring them over first-generation antihistamines because of their safety profile and proven efficacy in controlling the symptoms of urticaria. Also as in the JTF approach, the second step is increasing the dose of the non-sedating second-generation H1 antihistamines up to four times the recommended dose. The EAACI/WAO recommends reserving the addition of a leukotriene-modifying agent for cases of urticaria refractory to increased dosing of the second-generation H1 antihistamines. Addition of immunosuppressants and biologics is not recommended until the final step. Use of H2 antihistamines is not recommended in the EAACI/WAO algorithm. Both groups agree that short-term use of oral corticosteroids may be appropriate for management of exacerbations.

As previously discussed, the WAO/EAACI recommends frequent assessment of disease activity using the UAS as well as quality of life (QOL) to guide the stepwise approach whereas the JTF practice parameter discusses the importance of monitoring for severity at baseline and in between visits to assess treatment response but does not endorse specific disease severity or QOL instruments.

The WAO/EAACI endorses the potential for pseudoallergen-free diets to improve symptoms in CU despite the wide variability in response to this practice. The JTF does not support the use of pseudoallergen-free diets in the management of CU due to the low level of scientific evidence currently available to support their use.

There are many studies published on the treatment of chronic urticaria with immune-modulating drugs including

**Table 2** Comparison between urticaria guidelines

|                                                     | EAACI                                                      | JTF practice parameters                                    |
|-----------------------------------------------------|------------------------------------------------------------|------------------------------------------------------------|
| Evaluation for <i>Helicobacter pylori</i> infection | Recommended Extended Panel                                 | Not recommended                                            |
| Pseudoallergen-free diet                            | Recommended Extended Panel                                 | Not recommended                                            |
| ASST                                                | Recommended Extended Panel                                 | Not recommended                                            |
| LTRA                                                | Recommended third step                                     | Recommended second step                                    |
| Anti-H2 antihistamines                              | Not recommended                                            | Recommended second step                                    |
| First-generation antihistamines                     | Not recommended                                            | Recommended second and third steps                         |
| Systemic corticosteroids for exacerbations          | Up to 10 days                                              | 1–3 weeks                                                  |
| Other alternative therapies                         | Omalizumab recommended, others with low levels of evidence | Omalizumab recommended, others with low levels of evidence |

cyclosporine, dapsone, colchicine, and others. However, the evidence for use of these medications is considered weak due to the size of the study populations and/or the study design methodology. In addition, many of these medications have side effect profiles that may limit their use in patients with other concomitant medical problems such as hypertension, kidney disease, diabetes, blood dyscrasias, retinopathies, and hyperlipidemia. Additionally, none of these therapies have been FDA approved for treatment of chronic urticaria. However, there is sufficient evidence that these agents can be effective in subsets of patients with chronic urticaria refractory to antihistamines [26]. Although both the JTF and EAACI/WAO support short-term use of oral corticosteroids while attempting to achieve control with other agents, not surprisingly, there have been no controlled studies that have shown efficacy of systemic corticosteroids in CU. The majority of existing studies on immunosuppressants in chronic urticaria lack strength due to their small size, likely the result of poor funding support from both pharmaceutical companies and the NIH.

In 2014, the FDA approved the use of omalizumab, a humanized, monoclonal anti-IgE antibody previously approved for treatment of moderate to severe persistent asthma since 2003, for the treatment of chronic idiopathic urticaria not responsive to H1 antihistamines [33]. Dosing of omalizumab in asthma treatment is based on pre-treatment IgE level and the patient's weight. However, based on a number of dosing studies for omalizumab in the treatment of CIU, it was found that the doses of 150 and 300 mg administered subcutaneously once a month were more effective than 75 mg and placebo and not dependent on weight or total IgE levels. Clinical improvement has been reported as quickly as 1 week after the initial injection but may be delayed several weeks to months in others [18, 34•]. However, omalizumab has not been successful in induction of remission as symptoms have been demonstrated to quickly return after discontinuation [2•, 34•]. The known major risks associated with omalizumab include anaphylaxis, increased risk of cardiac and neurovascular events,

and a controversial increased risk of lymphoma [35–37]. Overall, based on the quality of evidence supporting omalizumab in contrast to the low risk of adverse effects related to its use, both the JTF and WAO/EAACI strongly endorse the use of omalizumab for those patients with refractory CU.

The EAACI/WAO practice parameter, but not the JTF practice parameter, addresses recommendations for the treatment of CU in children, as well as in pregnant and lactating women. For the treatment of CU in children, a strong recommendation was made to avoid first-generation H1 antihistamines because of their sedating effects. Only those second-generation H1 antihistamines that are efficacious and safe in the pediatric population (cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine) should be used as first-line therapy, and can be up-dosed in a weight-adjusted manner. For pregnant and lactating women, the recommendations are similar, although there is a lack in evidence that second-generation antihistamines, especially in higher than recommended doses, are safe in pregnancy. The FDA-approved doses of cetirizine, levocetirizine, and loratadine are category B while fexofenadine and desloratadine fall into category C [38]. Overall, the same treatment algorithm recommended in non-pregnant adults is advocated for children and pregnant or lactating women.

## Conclusion

Urticaria is a skin condition which whether acute or chronic can have a significant impairment on quality of life and well-being. Although there are many medications available which have been proven to successfully control the symptoms of urticaria in the majority of people, a portion of the population with chronic urticaria has long-standing uncontrolled disease. In addition, the current approved treatments only provide variable symptom control and do not lead to disease remission. Further research is needed to better elucidate the underlying

pathobiology of chronic urticaria so that safe and effective disease-modifying medications improve the management of this potentially debilitating disease. Until then, it is important to continue to build consensus regarding treatment algorithms based on available scientific evidence which is the purpose of clinical practice guidelines.

### Compliance with Ethics Guidelines

**Conflict of Interest** Jonathan A. Bernstein reports speaker fees from Genentech and clinical trial and IIS grants from Genentech/Novartis. Lauren M. Fine declares no conflict of interest.

**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.

### References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

- 1.•• Zuberbier T, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, Church MK, et al. The EAACI/GA2LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69:868–87. **This is the document outlining the European guidelines for urticaria.**
- 2.•• Bernstein JA, Lang DM, Khan DA, Craig T, Dreyfus D, Hsieh F, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol US Am Acad Allergy Asthma Immunol*. 2014;133:1270–7. **Published by Mosby, Inc. This is the document outlining the American guidelines for urticaria.**
3. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Giménez-Arnau A, et al. EAACI/GA2LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy Eur J Allergy Clin Immunol*. 2009;64:1417–26.
4. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al. Methods report on the development of the 2013 revision and update of the EAACI/GA(2) LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. 2014;69:e1–e29.
5. Shocket AL. Chronic urticaria: pathophysiology and etiology, or the what and why. *Allergy Asthma Proc*. 2006;27:90–5.
6. Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: associations found in a large population study. *J Allergy Clin*. 2012;129:1307–13. **ImmunolAllergy Clin Immunol Unit, Meir Medical Center, Kfar Saba, Israel. ronitco@clalit.org.il: American Academy of Allergy, Asthma & Immunology. Published by Mosby, Inc.**
7. Powell RJ, Du Toit GL, Siddique N, Leech SC, Dixon TA, Clark AT, et al. BSACI guidelines for the management of chronic urticaria and angio-oedema. *Clin Exp Allergy*. 2007;37:631–50. **Clinical Immunology Unit, Queen's Medical Centre, Nottingham, UK.**
8. Ap K. Chronic urticaria: pathogenesis and treatment. *J Allergy Clin Immunol*. 2004;114:465–74.
9. Chansakulporn S, Pongpreuksa S, Sangacharoenkit P, Pacharn P, Visitsunthorn N, Vichyanond P, et al. The natural history of chronic urticaria in childhood: a prospective study. *J Am Acad Dermatol*. 2014;71:663–8. **The natural history of chronic urticaria in childhood: a prospective study. Division of Allergy and Immunology, Department of Pediatrics, Srinakharinwirot University, Bangkok, Thailand; Division of Allergy and Immunology, Department of Pediatrics, Siriraj Hospital, Mahidol University, Bangkok, Thailand; Division of All (TRUNCATED: American Academy of Dermatology, Inc. Published by Elsevier Inc.**
10. Volonakis M, Katsarou-Katsari A, Stratigos J. Etiologic factors in childhood chronic urticaria. *Ann Allergy*. 1992;69:61–5.
11. Kauppinen K, Juntunen K, Lanki H. Urticaria in children. Retrospective evaluation and follow-up. *Allergy*. 1984;39:469–72.
12. Greenberger PA. Chronic urticaria: new management options. *World Allergy Organ J*. 2014;7:31–4551 – 7–31. **eCollection 2014. Division of Allergy-Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, 676 N. St. Clair Street, # 14108, 60611 Chicago, IL USA.**
13. Erbagci Z. The leukotriene receptor antagonist montelukast in the treatment of chronic idiopathic urticaria: a single-blind, placebo-controlled, crossover clinical study. *J Allergy Clin Immunol*. 2002;110:484–8. **Department of Dermatology, Gaziantep University Medical Faculty, Turkey.**
14. Grattan CE, O'Donnell BF, Francis DM, Niimi N, Barlow RJ, Seed PT, et al. Randomized double-blind study of cyclosporin in chronic "idiopathic" urticaria. *Br J Dermatol*. 2000;143:365–72. **Dermatology Centre, West Norwich Hospital, Norwich NR2 3TU, UK. clive.grattan@norfolk-norwich.thenhs.com.**
15. Mlynek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M. How to assess disease activity in patients with chronic urticaria? *Allergy*. 2008;63:777–80. **Department of Dermatology and Allergy, Charite-Universitätsmedizin Berlin, Berlin, Germany.**
16. Baiardini I, Pasquali M, Braidò F, Fumagalli F, Guerra L, Compalati E, et al. A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-QoL). *Allergy*. 2005;60:1073–8.
17. Mathias SD, Crosby RD, Zazzali JL, Maurer M, Saini SS. Evaluating the minimally important difference of the urticaria activity score and other measures of disease activity in patients with chronic idiopathic urticaria. *Ann Allergy Asthma Immunol*. 2012;108:20–4.
18. Saini S, Rosen KE, Hsieh HJ, Wong DA, Conner E, Kaplan A, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol*. 2011;128:567–73.e1. **Johns Hopkins Asthma and Allergy Center, Baltimore, MD 21224, USA. ssaini@jhmi.edu: American Academy of Allergy, Asthma & Immunology. Published by Mosby, Inc.**
19. Mlynek A, Magerl M, Hanna M, Lhachimi S, Baiardini I, Canonica GW, et al. The German version of the Chronic Urticaria Quality-of-Life Questionnaire: factor analysis, validation, and initial clinical findings. *Allergy*. 2009;64:927–36.
20. Valero A, Herdman M, Bartra J, Ferrer M, Jáuregui I, Dávila I, et al. Adaptation and validation of the Spanish version of the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL). *J Investig Allergol Clin Immunol [Internet]*. 2008;18:426–32. **Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19123433>.**
21. Platzer MH, Grattan CEH, Poulsen LK, Skov PS. Validation of basophil histamine release against the autologous serum skin test and outcome of serum-induced basophil histamine release studies in a large population of chronic urticaria patients. *Allergy Eur J Allergy Clin Immunol*. 2005;60:1152–6.

22. Konstantinou GN, Asero R, Maurer M, Sabroe RA, Schmid-Grendelmeier P, Grattan CE. EAACI/GA(2)LEN task force consensus report: the autologous serum skin test in urticaria. *Allergy*. 2009;64:1256–68. **Allergy and Clinical Immunology Department, NIMTS, Army Hospital and Allergy Research Center National & Kapodistrian University of Athens, Greece.**
23. Maurer M, Weller K, Bindeslev-Jensen C, Gimenez-Arnau A, Bousquet PJ, Bousquet J, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA(2)LEN task force report. *Allergy*. 2011;66:317–30. **Department of Dermatology and Allergy, Charite- Universitätsmedizin Berlin, Berlin, Germany. marcus.maurer@charite.de: John Wiley & Sons A/S.**
24. Quaranta JH, Rohr AS, Rachelefsky GS, Siegel SC, Katz RM, Spector SL, et al. The natural history and response to therapy of chronic urticaria and angioedema. *Ann Allergy*. 1989;62:421–4. **United States.**
25. Kozel MM, Mekkes JR, Bossuyt PM, Bos JD. Natural course of physical and chronic urticaria and angioedema in 220 patients. *J Am Acad Dermatol*. 2001;45:387–91. **Department of Dermatology, Academic Medical Center, University of Amsterdam, The Netherlands.**
26. Amin P, Levin L, Holmes SJ, Picard J, Bernstein JA. Investigation of patient-specific characteristics associated with treatment outcomes for chronic urticaria. *J Allergy Clin Immunol Pr*. 2015. doi: 10.1016/j.jaip.2014.12.007.
27. Ring J, Hein R, Gauger A, Bronsky E, Miller B. Once-daily desloratadine improves the signs and symptoms of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. *Int J Dermatol* [Internet]. 2001;40:72–6. **Available from:** <http://www.ncbi.nlm.nih.gov/pubmed/11277962> [http://apps.isiknowledge.com/full\\_record.do?product=UA&search\\_mode=GeneralSearch&qid=8&SID=T2FFQ4fEGczccZ8jE6Z&page=9&doc=419](http://apps.isiknowledge.com/full_record.do?product=UA&search_mode=GeneralSearch&qid=8&SID=T2FFQ4fEGczccZ8jE6Z&page=9&doc=419).
28. Staevska M, Popov TA, Kralimarkova T, Lazarova C, Kraeva S, Popova D, et al. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. *J Allergy Clin Immunol*. 2010;125:676–82. **Evidence supporting step 2 of both the JTF and EAACI guidelines to increase 2nd generation antihistamines up to 4 times the conventional dose. This is generally very effective, safe and easy to manage for many patients.**
29. Nettis E, Dambra P, D'Oronzio L, Loria MP, Ferrannini A, Tursi A. Comparison of montelukast and fexofenadine for chronic idiopathic urticaria. *Arch Dermatol*. 2001;137:99–100. **United States.**
30. Sanada S, Tanaka T, Kameyoshi Y, Hide M. The effectiveness of montelukast for the treatment of anti-histamine-resistant chronic urticaria. *Arch Dermatol Res*. 2005;297:134–8. **Department of Dermatology, Programs for Biomedical Research, Division of Molecular Medical Science, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3, Kasumi, Minami-ku, Hiroshima 734-8551, Japan.**
31. Nettis E, Colanardi MC, Paradiso MT, Ferrannini A. Desloratadine in combination with montelukast in the treatment of chronic urticaria: a randomized, double-blind, placebo-controlled study. *Clin Exp Allergy*. 2004;34:1401–7. **Department of Medical Clinic, Immunology and Infectious Diseases, Section of Allergy and Clinical Immunology, University of Bari, Bari, Italy. e.nettis@allergy.uniba.it.**
32. Bagenstose SE, Levin L, Bernstein JA. The addition of zafirlukast to cetirizine improves the treatment of chronic urticaria in patients with positive autologous serum skin test results. *J Allergy Clin Immunol*. 2004;113:134–40.
33. Presta LG, Lahr SJ, Shields RL, Porter JP, Gorman CM, Fendly BM, et al. Humanization of an antibody directed against IgE. *J Immunol*. 1993;151:2623–32.
34. Maurer M, Rosen K, Hsieh HJ, Saini S, Grattan C, Gimenez-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368:924–35. **Highlights the most efficacious dose of omalizumab (300 mg SC every 4 weeks) and the use of the UAS7 score to quantify response to treatment. Department of Dermatology and Allergy, Charite-Universitätsmedizin, Berlin.**
35. Strunk RC, Bloomberg GR. Omalizumab for asthma. *N Engl J Med*. 2006;354:2689–95. **Department of Pediatrics, Washington University School of Medicine, St. Louis, USA.**
36. Corren J, Casale TB, Lanier B, Buhl R, Holgate S, Jimenez P. Safety and tolerability of omalizumab. *Clin Exp Allergy*. 2009;39:788–97. **Allergy Research Foundation, Los Angeles, CA 90025, USA. jcorren@ucla.edu.**
37. Chiang DT, Clark J, Casale TB. Omalizumab in asthma: approval and postapproval experience. *Clin Rev Allergy Immunol*. 2005;29:3–16. **Division of Allergy and Immunology, Creighton University Medical Center, Omaha, NE, USA.**
38. Kar S, Krishnan A, Preetha K, Mohankar A. A review of antihistamines used during pregnancy. [Internet]. *J. Pharmacol Pharmacother*. 2012. p. 105–8. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3356948&tool=pmcentrez&rendertype=abstract>