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Urticaria and Atopic Dermatitis (M Furue and T Nakahara, Section Editors)

Review and Perspectives of the Recent International Guidelines on Treatment of Chronic Urticaria

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Abstract

Purpose of review Management of urticaria can be challenging, and various guidelines have been published by national and international societies. The most recent set of international guidelines, the EAACI/GA^{2}LEN/EDF/WAO guideline, seeks to define and classify urticaria as well as recommend diagnostic and therapeutic approaches in common subtypes of urticaria. This review aims to summarize treatment recommendations and provide additional perspectives on these recommendations.
Recent findings The EAACI/GA^{2}LEN/EDF/WAO guideline recommends a four-step approach to treatment of chronic urticaria: (1) second-generation antihistamines, (2) increase second-generation antihistamine up to fourfold, (3) add omalizumab, and (4) add cyclosporine. While cyclosporine has been determined to be effective in a recent meta-analysis, a careful analysis of the evidence indicates low-quality evidence.
Summary The most recent version of the EAACI/GA^{2}LEN/EDF/WAO guideline outlines definitions as well as diagnostic and treatment strategies for urticaria and its subtypes. While all of the recommendations are not agreed upon by all international allergy societies, there are many areas of consensus. Omalizumab is recommended before cyclosporine in the treatment algorithm. More studies are needed to provide further guidance with respect to alternative urticaria treatments.

Introduction

Urticaria is a mast cell/basophil-driven disease in which histamine and other mediators released from activated skin mast cells and/or basophils cause sensory nerve activation, vasodilation, plasma extravasation, and cell recruitment [1••, 2]. Many national and international guidelines have been developed on urticaria; for example, various societies including the World Allergy Organization [3], British Society for Allergy and Clinical Immunology [4], Asian Academy of Dermatology and Venereology Study Group/League of Asian Dermatological Societies [5], Argentine Association of Allergy and Clinical Immunology [6], Taiwanese Dermatological Association [7], Japanese Dermatological Association [8], and Skin Allergy Research Society of India [9] have published guidelines in recent years, taking somewhat different approaches to classification and management of urticaria. In general, acute spontaneous urticaria is defined as the presence of spontaneous wheals, angioedema, or both for less than 6 weeks, whereas in chronic urticaria, symptoms are present for greater than 6 weeks. While acute urticaria is more common, by nature, it resolves spontaneously and is less of a challenge to manage.

The focus of this review will be on recent guidelines and other systematic reviews regarding treatment of chronic urticaria.

2018 revised EAACI/GA^{2}LEN/EDF/WAO (international) guideline

In 2001, the first European guideline on management of urticaria was published [10]. Since then several revisions have been published in 2006 [11], 2009 [12], 2014 [13], and most recently in 2018 [1••]. In this review, we will refer to this most recent evidence and consensus-based guideline as the "international guideline." The international guideline was developed following the methods recommended by Cochrane and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group. The conference was held in December 2016 with participation from 48 delegates of 42 national and international societies, as a joint initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the EU-founded network of excellence, the Global Allergy and Asthma European Network (GA^{2}LEN), the European Dermatology Forum (EDF), and the World Allergy Organization (WAO). The aim was to update prior recommendations by synthesizing data and expert opinion from different countries regarding the understanding and management of urticaria, taking into consideration the fact that patient demographics and diagnostic/therapeutic options may vary across different parts of the world [1••].

Goals of therapy

Regarding treatment, the international guideline states that the goal of urticaria treatment should be complete symptom control. A multi-faceted approach is outlined, with identification and elimination of underlying causes, avoidance of eliciting factors, tolerance induction, and/or pharmacologic treatment. This consensus-based recommendation is founded on the basic pharmacologic principle of aiming at complete symptom relief, with use of as much medication as needed and as little as possible [1••]. Whether this is an achievable goal for most patients will be discussed later in this review.

Revised treatment algorithm for chronic urticaria

The international guideline developed a four-step algorithm (Fig. 1) for pharmacologic treatment of all forms of chronic urticaria, although it is mentioned that in some forms of inducible urticaria, on demand treatment (such as antihistamine taken 2 h prior to exposure) rather than continuous treatment may be appropriate.

Step 1: Regular use of second-generation antihistamines at licensed doses is recommended as first-line treatment of chronic urticaria [1••, 14]. This is consistent with the prior versions and other international guidelines.

Step 2: If symptom control remains inadequate after 2–4 weeks of therapy, the guideline suggests increasing the dosage of second-generation antihistamines up to fourfold [1••, 15, 16]. This step is also unchanged from the prior version. Despite the fact that many guidelines recommend updosing antihistamines as a second-line therapy, the evidence for this is neither consistent nor robust. A recent meta-analysis on updosing antihistamines in chronic urticaria revealed no differences in response rates or wheal number. There was a statistically significant improvement in pruritus, but the magnitude of this was small (0.13 on a scale of 0–3) [16]. A recent study from the Netherlands found that by updosing antihistamines with two separate antihistamines at fourfold dosages, a larger percentage of patients could achieve control. This led to a 49% reduction in need for third-line agents with a very limited increase in reported side effects [17•].

Step 3: Addition of omalizumab is recommended as third-line treatment at a dose of 300 mg every 4 weeks [1••, 18•], though different doses are approved in different countries. This recommendation was made based on a strong recommendation and > 90% consensus.

Step 4: If symptom control remains inadequate with any dose of antihistamine and omalizumab in combination, the guideline not only suggests addition of cyclosporine A within 6 months but also states that further

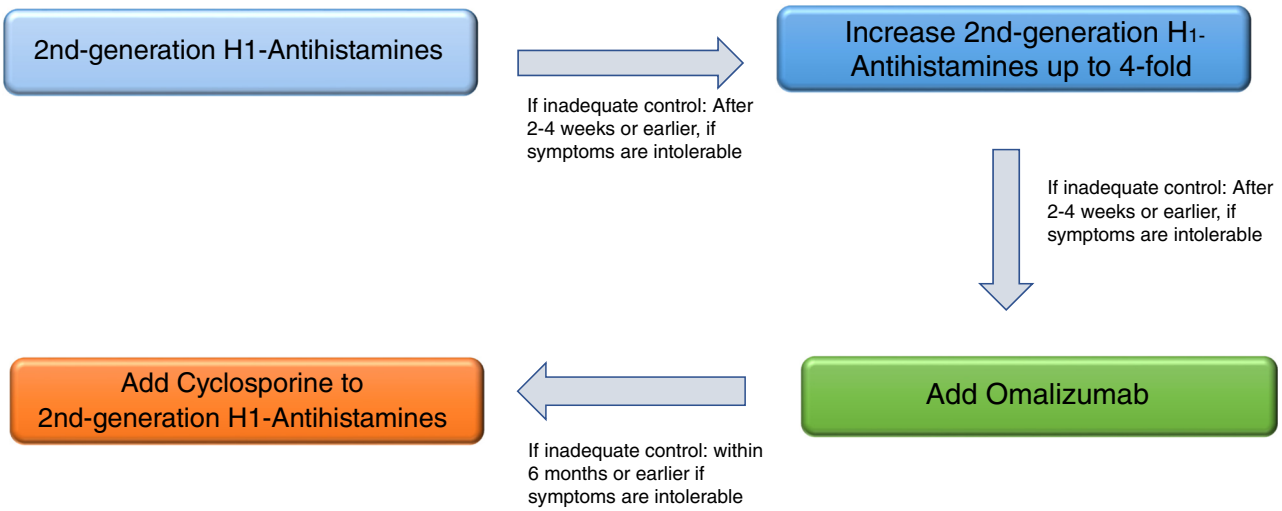

Fig. 1. The EAACI/GA(2)LEN/EDF/WAO recommended treatment algorithm for urticaria (Zuberbier et al., 2018).

recommendations cannot be made with respect to third-line treatment options. It is emphasized that cyclosporine should be trialed after omalizumab as cyclosporine is not licensed for use in urticaria and has an inferior side effect profile [1••]. Nevertheless, it has a preferable side effect profile to systemic corticosteroids. Systemic corticosteroids received a strong recommendation against use with a > 90% consensus.

These recommendations represent a major change from the prior 2014 version of the guideline, in which omalizumab, cyclosporine, and montelukast were listed as recommended third-line treatment options, with no specific recommendations as to the order in which they should be trialed [13]. Additional changes in this current European Guideline relate to other add-on medications to antihistamines often used in CU therapy. The guideline comments on the inability to make recommendations with respect to montelukast as an add-on treatment and indicate that in general the level of evidence for efficacy of leukotriene receptor antagonists is low but best for montelukast [19–21]. Similarly, no recommendations are made for or against combined use of H1 and H2 antagonists. It is stated that while both H2 antagonists and dapsone were recommended in previous versions of the guideline, there is now little evidence to maintain them in the recommended treatment algorithm. While third- and fourth-line treatment options are limited, UV-B, UV-A, and PUVA treatment for 1–3 months can be added to antihistamine treatment in cases of CSU and symptomatic dermographism [1••, 22]. A recent study shows that heparin or tranexamic acid may be effective in CSU patients with concurrent elevation in D-dimer levels [1••, 23].

Corticosteroids, while not recommended for long-term use, are suggested for acute exacerbations of chronic urticaria. The rationale for steroid use is that mast cell mediators other than histamine (such as platelet-activating factor, leukotrienes, cytokines) as well as a pronounced cellular infiltrate with basophils, lymphocytes, and eosinophils can contribute to symptoms and may respond completely to steroids but incompletely to antihistamines [1••, 2, 24]. Lastly, it is recommended that the need for treatment be re-evaluated every 3–6 months [1••].

The same treatment algorithm is suggested for use in children, as well as pregnant and lactating women, with caution. Although safety studies on increased dosage of second-generation antihistamines have not been done in pregnant women, to date, there have been no reports of birth defects in infants born to women using these medications. Use of omalizumab in pregnancy is thought to be safe and there have been no reports of teratogenicity [1••, 25•].

The guideline generally recommends against use of first-generation sedating antihistamines as first-line agents, although other guidelines (such as the WHO guideline ARIA) [26] express stronger opinions and recommend against use of first-generation antihistamines altogether. The antidepressant medication doxepin, anti-inflammatory medications dapsone and sulfasalazine, and immunosuppressant medications methotrexate and mycophenolate mofetil are not specifically discussed in the treatment algorithm but are mentioned in the context of widely used drugs that have low evidence for efficacy from publications but have been noted to be useful based on clinical experience [1••].

Discontinuation of medications (such as NSAIDs) that are suspected to worsen disease is recommended [1••, 27•]. Additionally, while some infections and chronic inflammatory processes have been implicated in CSU, the guideline comments on the difficulty of determining whether these are relevant causes of urticaria. Nevertheless, it is recommended that these conditions be treated, as many of them are also associated with malignancies. In patients with functional autoantibodies who are refractory to all other treatment, plasmapheresis is suggested; however, the evidence for this approach is weak [1••, 28]. For treatment of chronic inducible urticaria, the guideline states that avoidance of physical stimuli is desirable but difficult to achieve, as for many patients, there is a low threshold for symptom production via the relevant physical trigger. Induction of tolerance is thought to be useful in some subtypes of urticaria (such as cold, cholinergic, and solar urticaria), although again, maintenance is difficult to enforce from a practical standpoint. Avoidance of emotional and physical stress may be advised in some cases [29]. Avoidance is also mentioned in the context of IgE-mediated food allergy (which is a very rare cause of CSU) and pseudoallergenic reactions to naturally occurring food ingredients and/or food additives. A pseudoallergen-free or low histamine diet may be trialed although these diets are controversial and remain unproven in well-designed trials [1••, 30–32].

Effectiveness of a guideline-based approach to treatment

Given the recent publication of the EAACI/GA^{2}LEN/EDF/WAO guideline, studies utilizing this guideline-based approach to treatment have yet to be published. Sanchez et al. evaluated 150 patients who received treatment as per the step-wise algorithm outlined in the 2014 version of the EAACI guideline [13] and found a 92% success rate after 6 months of treatment. Fifty-eight percent of patients showed clinical response with first-line treatment (standard-dose anthistamines), which increased to 76% with second-line treatment (up to fourfold dose of antihistamines). Better control was achieved at 1 month than 2 weeks of first-line treatment. Third-line treatment consisted of either Xolair 300 mg/mo or cyclosporine 3 mg/kg/day for 4 months and led to good response in an additional 15% of patients (8% from the omalizumab group and 7% from the cyclosporine group). Response rates, measured via the DLQI (dermatology life quality index), were similar in omalizumab and cyclosporine groups, and "low"-dose cyclosporine was overall well tolerated [33•].

Perspectives and comparison of the international and US guidelines

In their recent publication, Zuberbier and Bernstein compared international vs. US perspectives on chronic urticaria based on the aforementioned most recent EAACI/GA^{2}LEN/EDF/WAO guideline and the US guideline (as represented by the 2014 AAAAI/ACAAI practice parameter) [34]. The two guidelines do not differ in their definitions of acute and chronic urticaria, and both the international and US guidelines include angioedema due to

the similar pathophysiology of wheals and angioedema. A few differences in terminology exist; for example, the US perspective uses the term physical urticaria (instead of inducible urticaria) and also the term "autoantibody-associated" urticaria (instead of autoimmune urticaria). The US guideline continues to use the term chronic idiopathic urticaria as opposed to chronic spontaneous urticaria. Additionally, while the US practice parameter does not specifically endorse a particular control or quality of life assessment, the more recent international guideline advocates for tools such as UAS7 (urticaria activity score), since evidence to support its use was available at the time of guideline publication[1••, 34–36].

With regard to treatment, the algorithm proposed by the AAAAI/ACAAI practice parameter also recommends initiating therapy with standard-dose second-generation antihistamines. However, multiple options for second-line treatment are provided, which include updosing of second-generation antihistamine, addition of another second-generation antihistamine, addition of a first-generation antihistamine, addition of a leukotriene receptor antagonist, and/or addition of an H2 antagonist. Third-line treatment includes add-on therapy with a potent antihistamine such as doxepin or hydroxyzine. Finally, fourth-line treatment includes a trial of omalizumab or cyclosporine, or other anti-inflammatory drugs, biologics, or immunosuppressants. The AAAAI/ACAAI practice parameter does not specifically recommend omalizumab prior to other immunosuppressants, biologics, or anti-inflammatory drugs [35]. However, since the time of publication, multiple studies have been published demonstrating efficacy and safety of omalizumab [25•, 37•, 38•, 39, 40•, 41, 42]. Key differences between the two guidelines are shown in Table 1.

AAAAI response to the EAACI/GA^{2}LEN/EDF/WAO guideline

While the AAAAI had representatives attend the conference that led to the development of this guideline, the AAAAI conditionally endorsed the guideline.

Table 1. Key differences between international and US guidelines for chronic urticaria

	International guideline	US guideline
Goal of treatment	Complete symptom control for all patients	Symptom control on a case-by-case basis
Intervals for escalation of therapy	2–4 weeks	Possibly longer than 2–4 weeks
Simultaneous use of different antihistamines	Discouraged	Not discouraged
Use of H2 blockers and leukotriene antagonists	No recommendations for or against use	Weak recommendation supporting use
Provocation threshold measurements in chronic inducible urticaria	Strong recommendation for use	Not widely used and limited evidence for benefit
Alternative agents included in algorithm	Omalizumab and cyclosporine	Omalizumab, cyclosporine, and other anti-inflammatory agents, biologics, or immunosuppressants

A letter to the editor by the AAAAI highlights management recommendations that differ from recommendations in these guidelines [43•]. Ten different management differences were discussed in this letter and a few of the key differences will be highlighted here. Firstly, regarding treatment, the international guideline states that the goal of treatment should be complete symptom control. While the AAAAI acknowledge that this is ideal, in the majority of patients, this goal may be unrealistic and may not actually be required to meet their needs and improve quality of life [18•, 44]. In clinical trials using omalizumab at 300 mg every 4 weeks, complete control that was sustained occurred in < 50% of patients [18•]. Thus, one should certainly evaluate patient preferences regarding risks and harm/burden when considering whether complete control is the appropriate goal for a given patient. Secondly, in the proposed treatment algorithm, the international guideline recommends escalating therapy at 2–4-week intervals from standard-dose antihistamines to fourfold dose antihistamines to omalizumab. The AAAAI supports the recommendation for regular assessment of disease activity, impact, and control; however, it is believed that these short-time intervals may lead to unnecessary escalation of therapy in some patients [33•]. Additionally, the international guideline recommends against simultaneous use of different antihistamines. While the AAAAI agrees that there is lack of high-quality evidence supporting use of different antihistamines, there may be some clinical benefit [17•] (for example, in patients who use a second-generation antihistamine during the day and a first-generation antihistamine at night). As previously mentioned, a recent study from the Netherlands found that by updosing antihistamines with two separate antihistamines at fourfold dosages, a larger percentage of patients could achieve control [17•]. This led to a 49% reduction in need for third-line agents with a very limited increase in reported side effects. The AAAAI also acknowledge that there is low-level evidence supporting addition of H2 antagonists and leukotriene antagonists to chronic urticaria treatment regimens [19–21, 45–50]. However, these agents are not costly and have very low side effect profiles. The guideline does not make a statement for or against use of these agents, but the AAAAI would argue for supporting use of these agents with a weak recommendation.

In patients who display inadequate response to omalizumab, the guideline suggests a trial of cyclosporine A, which, as evidenced by a meta-analysis performed by Kulthanan et al., has shown efficacy at low to moderate doses [51••]. However, other medications such as doxepin, methotrexate, mycophenolate mofetil, dapsone, and sulfasalazine are only mentioned in the context of being widely utilized but having limited evidence to support their use. This strategy appears to place disproportionate emphasis on cyclosporine use, while minimizing utility of other potentially beneficial therapies. There is also no mention of tacrolimus or vitamin D, both of which may provide some benefit in CSU [52, 53].

The AAAAI agrees with the limited use of diagnostic tests in CSU; however, the recommendation to use provocation threshold measurements in workup and management of all patients with chronic inducible urticaria appears somewhat problematic, in the sense that these tools are not widely available and there is limited evidence indicating that this practice leads to improved outcomes [54•]. Finally, the role of "pseudoallergen free" and low histamine diets in treating CSU has not been clearly established. While

CSU related to food additives can occur [55], there is a lack of high quality evidence showing that patients who show some level of response to "pseudoallergen free" diets truly have pseudoallergic food reactions as the underlying cause of their urticaria [30, 31].

Updated meta-analysis of cyclosporine for use in chronic Urticaria

In the treatment algorithm, the guideline suggests that cyclosporine be trialed after omalizumab. However, no recommendations are provided on dosing of cyclosporine or duration of treatment. A recent meta-analysis performed by Kulthanan et al. reviewed the efficacy and safety of off-label cyclosporine A (CsA) usage in CSU. Efficacy was assessed by the relative change in (UAS) at 4 weeks and response rates at 4, 8, and 12 weeks of treatment. Safety was assessed by analyzing the number of patients with one or more adverse events [51••].

The systematic review consisted of 18 studies (909 participants) receiving very low (< 2 mg/kg/day), low (2–4 mg/kg/day), or moderate (4–5 mg/kg/day) doses of CsA. Of these studies, two were randomized controlled trials (RCTs), one was an RCT switched to open-label prospective study, three were open-label prospective control studies, six were open-label prospective studies without controls, and six were retrospective studies. Of these, 12 total studies were included in the meta-analysis. Three studies were used to examine the relative change in UAS, and all 12 studies were used to examine response rates and safety profile. Very low, low, and moderate doses of CsA were studied in 7, 8, and 1 article, respectively. The duration of treatment ranged from 4 to 68 weeks [51••].

After 4 weeks of treatment, the mean relative change in UAS of CsA-treated patients was – 17.89, compared to – 2.3 in controls, which was significant. The overall pooled response rates to treatment with low to moderate doses of CsA at 4, 8, and 12 weeks was 54%, 66%, and 73%. Of note, no studies of very low dose CsA evaluated response rates at these time points. At 12 weeks of treatment, the pooled response rate for low dose CsA was 70%, compared to 83% for moderate dose CsA [51••].

With respect to safety, the rates of one or more adverse events in patients receiving very low, low, and moderate doses of CsA were 6%, 23%, and 57%, respectively, which was significant. Adverse events were categorized as major (specifically, hypertension or increased serum creatinine) or other. Major adverse events in patients treated with very low, low, and moderate doses of CsA were detected in 6%, 13%, and 10% of patients (not statistically different). Elevated serum creatinine due to CsA was found in 4.8% of patients with CSU, and hypertension was found in 5.8% of patients with CSU. Other adverse events (such as GI symptoms, headache, hirsutism, infection, paresthesias) were observed in 6%, 14%, and 46% of patients treated with very low, low, and moderate doses of CsA, which was statistically different. Of these, the most common adverse effect was GI symptoms, and most adverse events were mild and resolved with dose reduction. Adverse events that lead to discontinuation of CsA

included hypertension, severe GI symptoms, angina, persistent peripheral neuropathy, and severe headaches. Rates of discontinuation in the two studies from the meta-analysis that examined this were 5.9% [56] and 18.1% [57].

The two included studies that assessed quality of life (via the Dermatology Life Quality Index scores) did show improved quality of life in patients treated with CsA [57, 58]. CsA was reported to be beneficial in all included studies and more efficacious than placebo in the two studies that examined this. The 12 studies that reported relapse rates after CsA discontinuation reported relapse rates of 11–100% [51••]. One study assessed malignancy rates and found no increased rates of malignancy with long-term CsA treatment for up to 5–10 years. Additionally, no abnormal serum creatinine or high blood pressure was observed in patients with CSU on prolonged treatment of up to 10 years with very low doses of CsA [59].

The conclusion of this meta-analysis was that CsA is effective at low to moderate doses and that the safety profile is duration and dose dependent, with adverse events occurring in more than half of patients treated with moderate dose CsA. The article suggests that an appropriate dose for CsA in CSU ranges from 1 to 5 mg/kg/day and that 3 mg/kg/day should be an appropriate starting dose for most patients. Additionally, the pooled results of the study support continued treatment for up to 12 weeks in patients who initially do not respond well within 4 weeks of treatment. Treatment with low-dose CsA for 12 weeks was shown to significantly improve clinical severity in 70% of patients [51••]. Limitations of the study included the small number of trials included and limited quality of evidence. Key findings of this meta-analysis are shown in Table 2.

Disparities in assessment of evidence of cyclosporine for use in chronic urticaria

Overall, further studies are still needed to assess the benefit and long-term safety of cyclosporine treatment in chronic urticaria. As previously mentioned, very few randomized controlled trials with cyclosporine exist. Both the international and US guidelines used the GRADE approach to analyze evidence and make recommendations. Despite analyzing similar data, each guideline came to slightly different conclusions regarding level of evidence and strength of recommendation. The international guideline did not provide a specific GRADE level of evidence for cyclosporine but indicated it was efficacious in clinical trials and gave a conditional recommendation based on potential adverse effects. The US practice parameters provided a detailed analysis of the evidence revealing some methodological shortcomings in the few randomized controlled trials including no description of allocation concealment, heterogeneity of study participants, and enrollment of patients who had not failed up to fourfold dosing of antihistamines. These issues with both internal and external validity of the studies led to an assessment of the evidence as low quality (Table 2). Taking into account this level of evidence as well as potential for harm led to a weak recommendation by the US guidelines [35]. Disparities in assessment and

Table 2. Analysis of cyclosporine data in chronic urticaria

Key findings of meta-analysis	
Limitations	Comments
Small number of studies	Many limited quality
Only 2 RCT	Only 1 with severity assessment using UAS
Heterogeneous studies	2 RCTs, 3 open-label prospective control studies, 6 open-label prospective studies without controls, 2 retrospective studies
Effectiveness	
Dose dependent	Moderate doses (4–5 mg/kg/day) more effective than lower doses (2 to < 4 mg/kg/day)
Response rate may increase from 4 to 12 weeks of treatment	Consider longer treatment in those that do not respond to 4 weeks therapy
Recommend 3 mg/kg/day starting dose	At this dose ~ 70% response rate
Safety	
Dose dependent adverse effects	Independent of duration
Most adverse effects mild	Gastrointestinal symptoms most common, hypertension, paresthesia, headache, hirsutism, mild infection. Elevated creatinine in 4.8%
Key findings of GRADE analysis of cyclosporine RCT	
Quality assessment	
Risk of bias	Serious-very serious
Inconsistency	None serious
Indirectness	Yes
Imprecision	None (2/3 studies)
Overall quality	Low
Recommendation	Weak recommendation

recommendations of the same sets of data using the GRADE approach is not unique to chronic urticaria as pointed out in a recent review comparing evidence analysis in allergic rhinitis guidelines [60].

Conclusion

The most recent version of the EAACI/GA^{2}LEN/EDF/WAO guideline outlines definitions as well as diagnostic and treatment strategies for urticaria and its subtypes. While all of the recommendations are not agreed upon by all international allergy societies, there are many areas of consensus. Omalizumab is recommended before cyclosporine in the treatment algorithm based on the relatively larger amount of higher quality evidence supporting omalizumab use. More studies are needed to provide further guidance with respect to alternative urticaria treatments.

Compliance with Ethical Standards

Conflict of Interest
Shazia Lutfeali declares that she has no conflict of interest. David A. Khan declares that he has 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.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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