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Conflicts of interest

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Revisions to the international guidelines on the diagnosis and therapy of chronic urticaria

Summary

At the end of 2012, more than 300 participants discussed and agreed on the update of the international guidelines on urticaria at the 4th International Consensus Meeting (URTICARIA 2012). Currently, the recommendations are in the final process of international coordination. In preparation for the update, questions were prepared by an expert panel; this was followed by a systematic literature search. The questions and the resulting recommendations were discussed by the participants and decided upon in an open vote. Consensus was defined as at least 75% agreement. The updated guidelines will modify and improve the currently available guidelines in various areas, especially in therapy.

For the treatment of chronic urticaria, the new algorithm recommends a three-step process starting with a standard dose of a non-sedating H₁ antihistamine. If there is an insufficient treatment response, the dosage should be increased up to four times. In therapy refractory patients, omalizumab, cyclosporine A, or montelukast are advised in the third step. Short-term corticosteroid treatment for a maximum of 10 days may be considered. H₂ antihistamines and dapsone, which were included in the previous version of the guidelines, are absent in the updated and revised version because of changes in the evidence level.

Introduction

At the 4th International Consensus Meeting on Urticaria (URTICARIA 2012, November 2012 in Berlin), the international guidelines for the classification, diagnosis, and treatment of urticaria were revised and updated. During the two-day conference, more than 300 participants discussed the current recommendations regarding the nomenclature, classification, diagnosis, measurement of disease activity, as well as treatment of urticaria. Various updates were made and additional text was added using a consensus procedure. A panel of experts, consisting of international urticaria specialists, had formulated questions in advance and had conducted meta-analyses of the literature. As in the last version of the guidelines, the resulting suggestions for revising the recommendations were approved using the GRADE procedure for achieving consensus [1, 2], (Grading of Recommendations Assessment Development and Evaluation) [3]. Thus, the new recommendations are based on a systematic assessment of the data; they also include practical aspects which should facilitate treatment of urticaria patients in everyday practice.

Table 1 Changes in the guideline regarding the diagnostics and therapy of patients with urticaria.

Revisions	
Nomenclature and classification	Chronic urticaria occurs as chronic spontaneous urticaria or inducible urticaria. This group includes physical urticaria, cholinergic urticaria, contact urticaria, and aquagenic urticaria (Table 2); the term “chronic idiopathic urticaria” should be avoided.
Differential diagnosis	Differential diagnosis should include bradykinin-related angioedema and IL-1-associated urticarial syndromes (auto-inflammatory disorders, urticarial vasculitis).
Determining disease activity	New methods and instruments are available. <i>Disease activity:</i> UAS, AAS, determine threshold in inducible urticaria <i>Quality of life:</i> CU-Q _{oL} and AE-QoL
Diagnosis	In chronic spontaneous urticaria there is a two-step diagnosis: – Routine diagnosis (exclude severe underlying disease in all patients): ESR or CRP, blood differential, stop or switch from NSAIDs. – Further diagnosis (for identification and treatment of causes, in patients with long-standing and/or severe CSU): based on patient history, e.g., detection of autoreactivity, intolerance, infection. In chronic inducible urticaria, the diagnosis is limited (generally) to determining the trigger and the threshold
Therapy	Three-step algorithm: <i>Step 1:</i> non-sedating antihistamine <i>Step 2:</i> higher dosage of antihistamine <i>Step 3:</i> omalizumab, cyclosporine A, montelukast (Figure 2)
Abb.: UAS, urticaria activity score; AAS, angioedema activity score; CU-Q _{oL} , chronic urticaria quality of life survey; AE-QoL, angioedema quality of life survey	

The updated guidelines now contain recommendations which are supported by more than 25 national and international associations and professional societies. These recommendations will also be the basis for the revision of the German guidelines on the diagnosis and treatment of urticaria. The following review describes the revisions and improvements which were decided upon during the consensus meeting and which are part of the new international guidelines. The focus is on describing those recommendations which are relevant to everyday clinical practice (Table 1).

Definition, clinical picture, and differential diagnosis of urticaria

Urticaria is a term referring to a group of diseases which involve the onset of pruritic wheals, angioedema, or both. An exception is urticaria factitia (also known as symptomatic dermatographism). In this form of urticaria, there are wheals without angioedema. Another exception is pressure urticaria (also known as delayed pressure urticaria), which consists of deep swellings without the presence of wheals. Although some patients with chronic spontaneous urticaria have only wheals, the majority have both wheals and angioedema. Patients with chronic spontaneous urticaria rarely have isolated angioedema without wheals. In general, urticaria is easily diagnosed, given the typical appearance of skin changes and symptoms. Yet, physicians should recall that wheals and angioedema may occur in conjunction with other diseases as well.

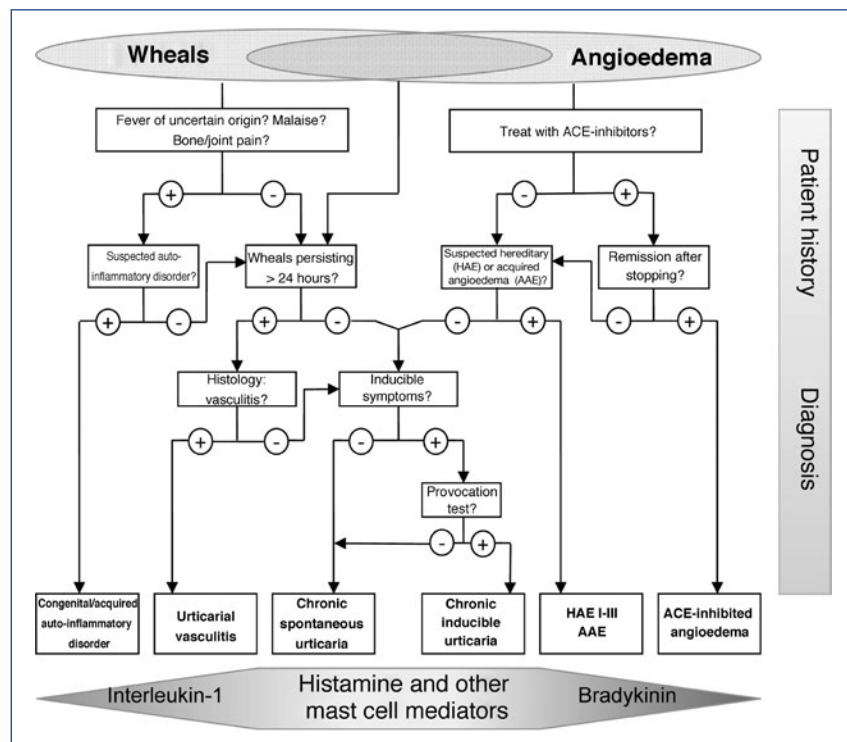


Figure 1 Algorithm for the diagnostic procedures in patients with wheals and/or angioedema.

Differential diagnoses should be considered in patients who have angioedema without wheals or wheals without angioedema.

In urticaria, wheals and angioedema are triggered by activation of mast cells in the skin and the subsequent release of mast cell mediators. Histamine plays an important role, although other mast cell mediators, such as leukotrienes and platelet-activating factor (PAF), are also involved in triggering symptoms. In auto-inflammatory disorders and urticarial vasculitis, wheals are triggered by other mechanisms. Thus, in patients who have only wheals, both diseases should be considered in the differential diagnosis. If only angioedema is present, other diseases, along with chronic urticaria, should also be considered. Unlike urticaria with associated angioedema, in patients with hereditary angioedema or angioedema due to ACE inhibitors, the symptoms are not triggered by mast cells or mast cell mediators, but by bradykinin.

The revised diagnostic algorithm for patients with wheals and/or angioedema (Figure 1) is a useful aid for the differential diagnosis of urticaria. Containing specific questions and tests, this five-step algorithm helps identify patients with auto-inflammatory diseases, urticarial vasculitis, and bradykinin-mediated angioedema. Patients with recurrent wheals, for instance, should be asked about malaise or bone/joint pain or recurrent fever of unknown cause. If so, an auto-inflammatory disorder, such as cryopyrin-associated periodic syndrome or Schnitzler syndrome, should be considered [4]. One should also ask whether individual wheals have been present for more than 24 hours, as this is a sign of urticarial vasculitis. If there is suspicion of urticarial vasculitis, a biopsy should be taken to confirm the diagnosis based on signs of vasculitis. Only after excluding the presence of an auto-inflammatory disorder or urticarial vasculitis may chronic urticaria be diagnosed in patients with recurrent wheals. Next, the physician should determine whether the patient has spontaneous or inducible urticaria.

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Table 2 Classification of chronic urticaria subtypes.

Chronic spontaneous urticaria (CSU)	Inducible urticaria
Spontaneous onset of wheals, angioedema, or both, for more than 6 weeks due to a known or unknown cause	▶ Physical urticaria – symptomatic dermographism¹ – Cold-induced urticaria² – Pressure urticaria³ – Solar urticaria – Heat-induced urticaria⁴ – Vibration-induced angioedema ▶ Cholinergic urticaria ▶ Contact urticaria ▶ Aquagenic urticaria
¹ Also known as urticaria factitia or dermographic urticaria, ² Also known as contact urticaria, ³ Also known as delayed pressure urticaria, ⁴ Also known as heat contact urticaria	

Distinguishing chronic urticaria from its differentials is crucial for proper treatment.

In patients with recurrent angioedema without wheals, it is equally important to recall the possibility of bradykinin-mediated angioedema. Hereditary angioedema, congenital angioedema (due to C1-inhibitor deficiency), and ACE-inhibitor angioedema are important differential diagnoses [4]. Obtaining specific information when taking the patient history or discontinuing ACE-inhibitor use, as well as simple laboratory tests (C4-inhibitor or C1-inhibitor concentration and function), are also useful for identifying or ruling out these diseases. Distinguishing chronic urticaria from its differentials is crucial for proper treatment. Antihistamines and other drugs which are otherwise successful in treating urticaria are ineffective in patients with auto-inflammatory diseases or bradykinin-mediated angioedema. Patients with auto-inflammatory disease are given interleukin-1 therapy; patients with bradykinin-mediated angioedema should be given icatibant (a bradykinin antagonist) or C1-inhibitors.

Classification of urticaria

Urticaria may be divided into acute and chronic forms. In acute urticaria, wheals and/or angioedema occur for 6 weeks at most; chronic urticaria is diagnosed if symptoms continue to develop for more than 6 weeks. Chronic urticaria is a common disease; the prevalence is around 1 %. This includes spontaneous and inducible types, as shown in Table 2. Chronic spontaneous urticaria is characterized by the onset of symptoms which are not caused induced by specific triggers, but rather are spontaneous. In recent years, various causes of chronic spontaneous urticaria have been described. It is now divided into types with a known cause and types of unknown origin. The previously used term “chronic idiopathic urticaria” should be avoided.

Chronic inducible types of urticaria may be divided into the physical types of urticaria (Table 2), cholinergic urticaria, contact urticaria, and aquagenic urticaria. The sub-types of chronic urticaria vary in terms of diagnosis and treatment. Thus in every patient with chronic urticaria it is essential to determine which type is present. In addition, various types of chronic urticaria may occur in the same patient.

Diagnosis of urticaria

Additional diagnostic tests should only be done in patients with severe and/or long-term chronic spontaneous urticaria.

The diagnostic procedures in patients with acute urticaria are fundamentally different from those used in patients with chronic urticaria. There are also significant differences in the diagnostic procedure in patients with chronic spontaneous urticaria and chronic inducible urticaria. The current guideline recommendations are thus based on a precise formulation of the goals and steps in the recommended diagnostics. In acute urticaria, no causal diagnostics are advised. The reason is that spontaneous remission of acute urticaria is very likely and that often one can identify a cause in the patient's history (acute infection, medications, foodstuffs, etc.). Additional diagnostic testing should only be performed if an allergy is suspected. This can help the patient avoid future exposure to the triggering allergens. In chronic spontaneous urticaria, the diagnostic procedure is different. It consists of two steps: first, all patients with chronic spontaneous urticaria are tested for serious inflammatory disease (ESR/CRP and blood differential), and potential triggering drugs such as non-steroidal anti-inflammatory drugs (NSAID) are discontinued. The second step is reserved for patients with severe and/or long-term chronic spontaneous urticaria and involves searching for a cause using additional diagnostic tests. Depending on the patient's history, he or she should be tested for autoreactivity, food intolerance, and chronic infections. Unlike chronic spontaneous urticaria, the causes of chronic inducible urticaria are largely unknown. Thus, both detecting the trigger and determining the threshold are central to the diagnostic procedure. If there is suspicion of cold-induced urticaria, a skin provocation test should be performed, and if the result is positive, the threshold should be identified. The same applies to urticaria factitia/ symptomatic dermographism, heat-induced urticaria, pressure urticaria, and solar urticaria.

Therapy of urticaria

The goal of treatment of urticaria is to completely alleviate the symptoms, regardless of whether this is done using causal therapy or symptomatic treatment. Before initiating treatment, disease activity must be determined. In patients with chronic spontaneous urticaria, the disease activity may be determined using the urticaria activity score (UAS) [5]. This simple, validated test allows for measurement of disease activity over the course of disease and for an assessment of treatment success. The UAS is recommended in the current guidelines as a standard instrument; it is based on daily documentation by the patient of his or her symptoms. Every day for 7 days, the patient should write down the number of wheals in the past 24 hours as well as the intensity of itching. No wheals = 0; up to 20 wheals = 1; 20 to 50 wheals = 2; and 50 or more = 3. In the same manner, pruritus is given 3 points for severe itching, 2 for moderate itching, 1 for mild itching, and 0 if there is none. The daily scores (0–6) are added together to arrive at a weekly (UAS 7) score (0–42 points). For determining disease activity in patients with angioedema, along with the UAS, the angioedema activity score is recommended [6]. In addition, surveys on the quality of life should also be used to determine its level of impairment in such patients. The “Chronic Urticaria Quality of Life” (CU-Q2oL) questionnaire [7] and the “Angioedema Quality of Life” (AE-QoL) questionnaire [8] are recommended. Symptomatic treatment of urticaria is based on a revised stepwise treatment scheme (Figure 2). As in the previous version of the guidelines, non-sedating antihistamines (standard dosage) are the first-line treatment. The antihistamine should be taken as preventive therapy, i.e., on a daily basis. In patients who do not respond

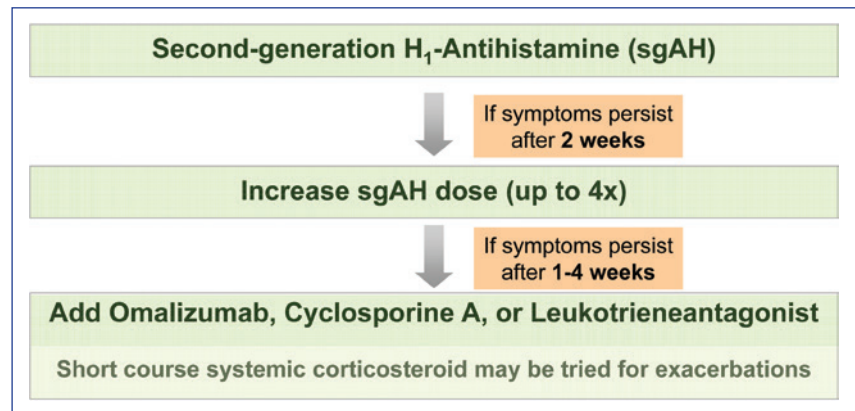


Figure 2 Treatment algorithm for chronic urticaria.

adequately to standard dosages of non-sedating antihistamines, the dosage should be increased after a maximum of two weeks, up to four times the standard dosage. This procedure is supported by current studies which show that higher dosages are safe and the response superior to standard dosages. Patients who fail to respond adequately even to higher dosages of non-sedating antihistamines should be given omalizumab (anti-IgE) [9–12], cyclosporine A [13–17], or montelukast (leukotriene antagonist) [18–20]. The recommendation from the previous guidelines on the use of H₂ antihistamines and dapsone is no longer considered a standard therapy due to new evidence. Except for standard dosages of antihistamines, all of these therapies are off-label treatments. For any treatment, it is advisable to occasionally check for spontaneous remission by temporarily discontinuing the drug.

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