



Urticaria: an update on diagnostics, therapy, and differential diagnosis

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Abstract Urticaria is a common skin disorder that can occur at any age; middle-aged women are most commonly affected. The diagnosis of urticaria is straightforward: the clinical picture includes wheals and/or angioedema accompanied by extreme itch. As a general rule, a wheal lasts for up to 1 day, whilst mast cell-mediated angioedema can remain symptomatic for up to 2 days. A distinction is made between acute and chronic forms (≥ 6 weeks), whereby symptoms may be present every day. Relapsing disease courses have also been described. This paper presents a current overview.

Urticaria requires a detailed patient history and appropriate diagnostic methods in order to establish the diagnosis accurately. There are more than 10 subtypes of this disorder, which can also occur as a combined form. A distinction is made between two main groups: spontaneous and inducible forms of urticaria. Acute urticaria is the most common form. A search for the cause is only necessary in the case of long-term and severe disease. The symptomatic treatment of urticaria should be performed parallel to the search for its cause. Any possible causes/trigger factors that are identified can be treated/remedied or eliminated. Urticaria then resolves or regresses after only a few weeks. Spontaneous remissions are possible. Only one extremely rare subgroup of cold urticaria shows a familial aggregation. No other forms of urticaria are inherited.

Keywords Urticaria · Chronic urticaria · Spontaneous urticaria · Inducible urticaria · Burden of disease · Management

Abbreviations

AAS	Angioedema activity score
AE-QoL	Angioedema quality of life questionnaire
ASST	Autologous serum skin test
CU-Q2oL	Chronic urticaria quality of life questionnaire
HADS	Hospital anxiety and depression scale
IgE	Immunoglobulin E
UAS	Urticaria activity score
UCT	Urticaria control test

What is the typical disease course?

Patients complain of sudden-onset, itchy wheals and/or generally painful/burning angioedema (Figs. 1 and 2). Symptoms may appear where mast cells are found, i. e. on the skin and mucosa. As in many skin disorders, stress can increase disease activity.

In a first step, it is important to establish from the patient history whether urticaria is spontaneous, inducible, or a combination of these two types (Table 1).

With the exception of the rarely described familial cold urticaria, urticaria occurs spontaneously. This means that: the susceptibility to develop the disorder is not inherited. The most common form is acute spontaneous urticaria, which persists for only a few days to weeks. Most patients with chronic spontaneous urticaria are symptom-free after 6 months at the latest. In addition to investigating the cause, the management of urticaria should include appropriate treatment from the outset. This helps to reduce or avoid socioeconomic costs, e. g., due to fewer outpatient visits, inpatient admissions, or work absences.

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Fig. 1 Angioedema

Patients and physicians can find information and support at www.urtikaria.net [1–4].

Subtypes of urticaria and differential diagnoses

Acute urticaria is the commonest form, affecting every fourth person in the course of their life. Urticaria that lasts for longer than 6 weeks is considered chronic. It can be classified into spontaneous, inducible, and combined forms (Table 1). Particularly common inducible forms include: symptomatic dermographism (or urticaria factitia), cold urticaria (following contact with cold), and cholinergic urticaria (small wheals that rapidly occur upon an increase in core body temperature). Spontaneous and inducible urticaria occur concomitantly in around 25% of cases.

With the spontaneous form, patients complain of the appearance of wheals and/or angioedema of no known cause. Stress exacerbates the symptoms. Possible causes include: autoreactive phenomena in combination with autoimmune disorders (e.g., thyroiditis); food intolerances, such as histamine intolerance; pseudo-allergy to preservatives and/or colorings; or infections (e.g., in the gastrointestinal tract due to *Helicobacter pylori* or *Yersinia*). Once possible causes have been remedied or eliminated, urticaria symptoms diminish gradually and ultimately disappear completely. There is also a subform in which the cause or trigger is unknown: urticaria of unknown etiology (Table 2).

The clinical presentation of urticaria is unambiguous. In terms of differential diagnoses, disorders asso-

ciated with urticarial skin changes should be considered. The duration of individual eruptions is relevant here. Skin changes that have been present for longer than 24 h, are markedly indurated, hemorrhagic, bullous, and/or healing with hyperpigmentation prompt suspicion of urticarial vasculitis, vesiculobullous disorders, or eosinophilic cellulitis. Mastocytosis can also strongly manifest as urticaria. As a general rule, a biopsy including direct immunofluorescence can provide further diagnostic information.

Urticarial eruptions are often described within the large group of auto-inflammatory syndromes. Co-symptoms such as fatigue, joint pain, bouts of fever, and elevated inflammatory markers (during bouts) are key to diagnosis. In the case of angioedema without urticarial eruptions, mast cell-related angioedema needs to be distinguished from all other forms of non-mast cell-related angioedema. The duration of angioedema (>2 days), pronounced abdominal attacks, and failure to respond to high-dose corticosteroids and/or antihistamines generally point to bradykinin-mediated angioedema.

Diagnostic work-up for spontaneous urticaria

The acute form does not require an extensive diagnostic work-up. Infections and possible (pseudo-)allergic reactions to foods or drugs (e.g., non-steroidal anti-inflammatory drugs) need to be ruled out on the basis of patient history.

A thorough search for the cause of urticaria is recommended if the disease persists for several months, is severe, and/or responds poorly to drugs such as antihistamines. As a basic principle, however, diagnostic tests for inflammation should be performed in order to rule out differential diagnoses such as auto-inflammatory syndromes (e.g., Schnitzler syndrome) (Fig. 2; Table 2).

Common causes/trigger factors:

- Infections of the ear, nose, throat, and dental regions, *Helicobacter pylori*, or, more rarely, *Yersinia* infection; symptoms recede after only a few weeks.
- Intolerance reactions to preservatives and/or colorings (pseudo-allergens) and/or histamine-rich food, as well as histamine liberators; dietary intervention for at least 3 weeks is recommended (dietary models: www.urtikaria.net). Keeping a symptom diary is advisable [5, 6].
- The autoreactive subform of chronic spontaneous urticaria is frequently associated with other autoimmune diseases such as thyroiditis. Therefore, an autologous serum skin test (ASST), which is key to diagnosis, should be performed. Patient serum is injected intracutaneously. Histamine and sodium chloride solutions serve as positive and negative controls.
- Type I allergies are rare in chronic urticaria. If a type I allergy is suspected, keeping a symptom

Fig. 2 Diagnostic scheme. (AE angioedema, RAS renin-angiotensin system, AH antihistamine, DD differential diagnosis)

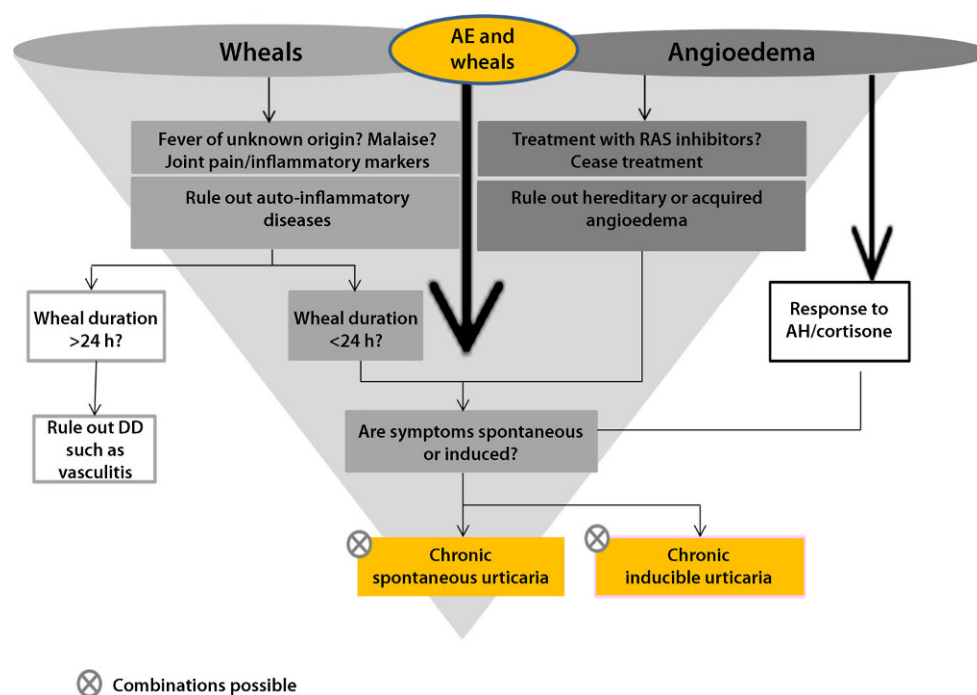


Table 1 Subtypes of urticaria

Spontaneous urticaria	Inducible/provocable urticaria
Acute or chronic (>6 weeks)	
Spontaneous onset of wheals and/or angioedema due to known or unknown causes	Symptomatic dermographism (Urticaria factitia)
	Cold urticaria
	Delayed pressure urticaria
	Solar urticaria
	Heat urticaria
	Vibratory urticaria
	Cholinergic urticaria
	Contact urticaria
	Aquagenic urticaria
Combinations of spontaneous and inducible forms are not uncommon	

and dietary diary is helpful. Auto-allergic phenomena are the subject of discussion.

- In the case of suspected inducible urticaria, standardized physical tests are ideally used to confirm the diagnosis (Table 3; [7, 8]).

Determining disease burden

Disease burden is defined as the extent of disease activity and its effect on quality of life. Since the disease does not always show the same intensity and may occur recurrently (e.g., angioedema), it is advisable to keep a symptom calendar. Quality of life should be measured concomitantly.

A standardized questionnaire has proved its worth for the purposes of disease classification, particularly in the case of longstanding disease (www.urtikaria.net).

Table 2 Diagnostic work-up of subtypes of spontaneous urticaria

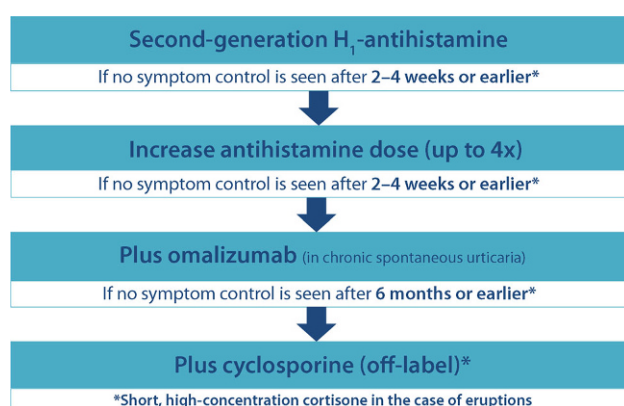
Routine diagnostic investigations	
Acute spontaneous urticaria	No further diagnostic investigations
	Patient history: infections, suspected adverse reaction to food, drugs—requires investigation
Chronic spontaneous urticaria	Rule out severe underlying inflammatory disease: determine erythrocyte sedimentation rate, C-reactive protein, differential blood count (creatinine, liver enzymes)
	Discontinue suspected drugs (particularly NSAR ^a)
Advanced diagnostic program for severe or long-term csU ^b	
Acute spontaneous urticaria	No diagnostic investigations
Chronic spontaneous urticaria	Search for cause: autoreactivity, autologous serum test, chronic infections (dental or ENT region, Helicobacter, Yersinia), food intolerances
	Causal treatment where appropriate
^a Non-steroidal anti-inflammatory drugs	
^b Chronic spontaneous urticaria	

The validated, weekly urticaria activity score (UAS7) and the angioedema activity score (AAS) are available to measure disease activity. For the sake of thoroughness, it is especially important to determine quality of life when first changing to systemic treatments: validated, disease-specific questionnaires are available to this end (CU-Q2oL, AE-QoL). The urticaria control test (UCT) has proven its worth in daily practice and over the course of disease. Four questions are used to measure disease activity and quality of life, thereby determining disease burden. A special questionnaire is available for cases where comorbidities

Table 3 Diagnostic work-up for subtypes of inducible urticaria

	Provocation testing	Complementary investigations
<i>Cold urticaria</i>	Cold provocation and swelling tests (TempTest®, ice cube, cold water, cold wind)	Differential blood count and ESR ^a or CRP ^b , cryoproteins to rule out other diseases (especially infections)
<i>Delayed pressure urticaria</i>	Pressure test and threshold test	None
<i>Heat urticaria</i>	Heat provocation test and threshold test	None
<i>Solar urticaria</i>	Testing with UV light and visible light of varying wave-lengths and threshold test	Rule out other light-induced dermatosis
<i>Symptomatic dermographism</i>	Dermographic tester and threshold test (FricTest®)	Differential blood count, ESR or CRP
<i>Vibratory urticaria</i>	Test, e. g., with a vortex	None
<i>Aquagenic urticaria</i>	Application of a wet cloth (at body temperature) to the skin for 20 min	None
<i>Cholinergic urticaria</i>	Sports and “hot bath” provocation test	None
<i>Contact urticaria</i>	Cutaneous provocation test, skin test with immediate reading, e. g., skin prick test	None

^aErythrocyte sedimentation rate
^bC-reactive protein

**Fig. 3** Management of urticaria (according to the guideline of the EEACI/GA(2)LEN/EADF/WAO 2016)

such as depression or anxiety are suspected (hospital anxiety depression scale, HADS) [9].

Management of urticaria

Parallel to diagnostic investigations (the search for causes and triggers), it is essential to initiate symptomatic treatment from the outset for all subtypes of urticaria. Second generation antihistamines are available as the first-line treatment. As a general rule in severe forms of urticaria, disease burden should be determined prior to starting medication in order to permit an objective assessment of response in the further course. If the recommended daily dose of antihistamines fails to control symptoms, it is advisable to increase the daily dose by up to four-fold over 2–4 weeks (weight-adjusted in children) [10–13]. Where necessary, the antihistamine can be changed [10]. Should this also fail to achieve a satisfactory reduction in symptoms, adjunctive omalizumab therapy is indicated in chronic spontaneous urticaria or in combined forms (300 mg/week subcutaneously from the age of 12 years). In such cases, dosage is

set irrespective of IgE, in contrast to allergic asthma [14–16]. A reduction in IgE receptors was observed in chronic spontaneous urticaria over the course of treatment [17]. Other trials with biologic agents are currently under clinical development [18]. In the case of severe eruptions, it may be necessary at any stage of disease to administer high-concentration cortisone (prednisolone-equivalent 0.5–1 mg/kg body weight, no tapering) [19].

Treatment with omalizumab is also effective in antihistamine-resistant, inducible subforms of urticaria [20, 21]. However, omalizumab is not approved for these subforms, and an application needs to be submitted to the relevant health insurance fund for reimbursement. Alternatively, several other immunomodulatory drugs are available, e. g., cyclosporine (Fig. 3; [22]). The recommendations given in the Embryotox database should be followed in the case of pregnant or nursing women. Loratadine or cetirizine are recommended in such cases (as of June 2017). There are no recommendations at present on the use of omalizumab during pregnancy or nursing (www.embryotox.org).

Conclusion

The clinical picture provides the key to diagnosis. The management of urticaria is straightforward. Treatment and diagnosis should be performed in parallel. Using validated disease-specific questionnaires, it is possible to objectively determine disease burden.

The diagnosis requires review if patients continue to experience symptoms despite a search for the cause and intensified treatment; where appropriate, patients should present to an urticaria center. Patients and physicians can find advice and support at www.urtikaria.net.

Conflict of interest P. Staubach declares that she has no competing interests in this publication.

References

1. Beck LA, Bernstein JA, Maurer M. A review of international recommendations for the diagnosis and management of chronic urticaria. *Acta Derm Venereol*. 2017;97:149–58.
2. Maurer M, Staubach P, Raap U, Richter-Huhn G, Bauer A, Rüeff F et al. H1-antihistamine-refractory chronic spontaneous urticaria: it's worse than we thought—first results of the multicenter real-life AWARE study. *Clin Exp Allergy*. 2017;47:684–92.
3. Staubach P, Zuberbier T, Vestergaard C, Siebenhaar F, Toubi E, Sussman G. Controversies and challenges in the management of chronic urticaria. *J Eur Acad Dermatol Venereol*. 2016;30:16–24.
4. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al. The EAACI/GA(2)LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69:868–87.
5. Magerl M, Pisarevskaja D, Scheufele R, Zuberbier T, Maurer M. Effects of a pseudoallergen-free diet on chronic spontaneous urticaria: a prospective trial. *Allergy*. 2010;65:78–83.
6. Wagner N, Dirk D, Peveling-Oberhag A, Reese I, Rady-Pizarro U, Mitzel H, et al. A Popular myth—low-histamine diet improves chronic spontaneous urticaria—fact or fiction? *J Eur Acad Dermatol Venereol*. 2017;31:650–5.
7. Magerl M, Altrichter S, Borzova E, Giménez-Arnau A, Grattan CE, Lawlor F et al. The definition, diagnostic testing, and management of chronic inducible urticarias—The EAACI/GA(2)LEN/EDF/UNEV consensus recommendations 2016 update and revision. *Allergy*. 2016;71:780–802.
8. Abajian M, Schoepke N, Altrichter S, Zuberbier T, Maurer M. Physical urticarias and cholinergic urticaria. *Immunol Allergy Clin North Am*. 2014;34:73–88.
9. Staubach P, Groffik A. Useful tools for documenting urticaria. *Hautarzt*. 2013;64:650–5.
10. Termeer C, Staubach P, Kurzen H, Strömer K, Ostendorf R, Maurer M. Chronic spontaneous urticaria—a management pathway for patients with chronic spontaneous urticaria. *J Dtsch Dermatol Ges*. 2015;13:419–28.
11. Church MK, Maurer M, Simons FE, Bindslev-Jensen C, van Cauwenberge P, Bousquet J, et al. Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. *Allergy*. 2010;65:459–66.
12. Sharma M, Bennett C, Carter B, Cohen SN. H1-antihistamines for chronic spontaneous urticaria: an abridged cochrane systematic review. *J Am Acad Dermatol*. 2015;73:710–716.e4.
13. Ott H. Chronic urticaria in childhood: rational diagnostics and treatment. *Hautarzt*. 2017;68:571–82.
14. Maurer M, Rosén K, Hsieh HJ. Omalizumab for chronic urticaria. *N Engl J Med*. 2013;368:2530.
15. Maurer M, Rosén K, Hsieh HJ, Saini S, Grattan C, Giménez-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368:924–35.
16. Staubach P, Metz M, Chapman-Rothe N, Sieder C, Bräutigam M, Canvin J, et al. Effect of omalizumab on angioedema in H1-antihistamine-resistant chronic spontaneous urticaria patients: results from X-ACT, a randomized controlled trial. *Allergy*. 2016;71:1135–44.
17. Metz M, Staubach P, Bauer A, Brehler R, Gericke J, Kangas M, et al. Clinical efficacy of omalizumab in chronic spontaneous urticaria is associated with a reduction of FcεRI-positive cells in the skin. *Theranostics*. 2017;7:1266–76.
18. Harris JM, Cabanski CR, Scheerens H, Samineni D, Bradley MS, Cochran C, et al. A randomized trial of quilizumab in adults with refractory chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2016;138:1730–2.
19. Peveling-Oberhag A, Reimann H, Weyer V, Goloborodko E, Staubach P. High-concentration liquid prednisolone formula: filling a therapeutic niche in severe acute attacks of urticaria and angioedema. *Skin Pharmacol Physiol*. 2016;29:9–12.
20. Metz M, Schütz A, Weller K, Gorczyza M, Zimmer S, Staubach P, et al. Omalizumab is effective in cold urticaria—results of a randomized placebo-controlled trial. *J Allergy Clin Immunol*. 2017;140:864–7.
21. Maurer M, Schütz A, Weller K, Schoepke N, Peveling-Oberhag A, Staubach P, et al. Omalizumab is effective in symptomatic dermographism—results of a randomized placebo-controlled trial. *J Allergy Clin Immunol*. 2017;140:870–873.e5.
22. Holm JG, Ivyanskiy I, Thomsen SE. Use of nonbiologic treatments in antihistamine-refractory chronic urticaria: a review of published evidence. *J Dermatolog Treat*. 2017;31:1–18.