

Original article

EAACI/GA²LEN/EDF guideline: definition, classification and diagnosis of urticaria

This guideline is the result of a consensus reached during a panel discussion at the 2nd International Consensus Meeting on Urticaria, Urticaria 2004, a joint initiative of the European Academy of Allergology and Clinical Immunology Dermatology Section and the European Union (EU)-funded network of excellence, GA²LEN. It covers the definition and classification of urticaria, taking into account the recent progress in identifying causes, eliciting factors and pathomechanisms of this disease. We have outlined useful diagnostic approaches for different subtypes of urticaria. This guideline was, in addition, accepted by the European Dermatology Forum (EDF) and was formally approved by the European Union of Medical Specialists (UEMS).

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This guideline is the result of a panel discussion during the 2nd International Meeting on Urticaria – Urticaria 2004, a joint initiative of the EAACI Dermatology Section and GA²LEN. As members of the panel the authors had prepared their suggestions regarding the definition, classification and routine diagnosis of urticaria in advance, based on the existing consensus paper of the first symposium in 2000 (1). These suggestions were then

discussed in detail among the panel and with the participants of the meeting, to achieve a consensus using a simple voting system where appropriate. The participation of more than 400 specialists in urticaria from over 20 countries ensured that this consensus includes European regional differences in viewpoint and provides a basis for improved comparison of future studies in the field of urticaria.

Urticaria is widely regarded as a heterogeneous group of diseases/disorders/conditions that share a distinct skin reaction pattern, i.e. the development of urticarial skin lesions. The wide diversity and number of different urticaria subtypes that have been identified reflect, at least in part, our increasing understanding of the causes and eliciting factors of urticaria and the molecular and cellular mechanisms involved in its pathogenesis. The aim of this guideline is to provide an updated definition and classification of urticaria, thereby facilitating the interpretation of divergent data from different centres regarding eliciting causes and therapeutic responsiveness of subtypes of urticaria. Furthermore, this guideline provides recommendations for diagnostic approaches in common subtypes of urticaria.

Definition

Clinical appearance

Urticaria is characterized by the rapid appearance of wheals and/or angioedema (Fig. 1).

A wheal consists of three typical features: (i) a central swelling of variable size, almost invariably surrounded by a reflex erythema; (ii) associated itching or sometimes burning sensations and (iii) a fleeting nature, with the skin returning to its normal appearance, usually within 1–24 h.

Angioedema is characterized by: (i) sudden, pronounced swelling of the lower dermis and subcutis; (ii) sometimes pain rather than itching; (iii) frequent involvement of mucous membranes and (iv) resolution that is slower than for wheals and can take up to 72 h.

Histological aspects

On histology, the classical fleeting wheal demonstrates oedema of the upper and mid-dermis, with dilatation of the postcapillary venules and lymphatic vessels of the upper dermis. In angioedema, similar changes occur primarily in the lower dermis and the subcutis. Skin affected by wheals virtually always exhibits upregulation of endothelial adhesion molecules and a mixed inflammatory perivascular infiltrate of variable intensity, consisting of neutrophils and/or eosinophils, macrophages and T-helper lymphocytes (2). A mild to moderate increase of mast cell numbers has also been observed. In delayed pressure urticaria, the infiltrate is typically located in the mid to lower dermis (3). In some subtypes of urticaria, upregulation of adhesion molecules (4) and altered cytokine expression are also seen in uninvolved skin (5).

These findings underline the complex nature of the pathogenesis of urticaria which has many features in addition to the release of histamine from dermal mast cells. These changes are also seen in a wide variety of inflammatory reactions and are thus not specific or of diagnostic value. A search for more specific histological markers for different subtypes of urticaria is desirable.

Classification of urticaria on the basis of its duration, frequency and causes

The spectrum of clinical manifestations of different urticaria subtypes is very wide. Additionally, two or

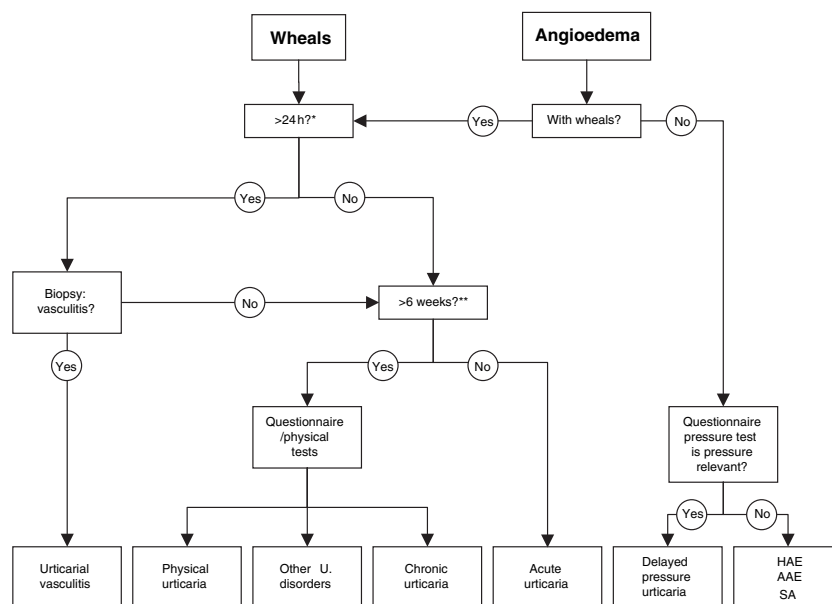


Figure 1. Differential diagnosis of urticarial symptoms. HAE, hereditary angioedema; AAE, acquired angioedema with C1 esterase inhibitor deficiency; SA, spontaneous angioedema as manifestation of chronic urticaria with only deep swellings but no superficial wheals. *Duration of individual wheals; **duration of urticaria.

Table 1. Classification of urticaria

Group	Subgroup	Definition
Spontaneous urticaria	Acute urticaria	Spontaneous wheals <6 weeks
	Chronic urticaria	Spontaneous wheals >6 weeks
Physical urticaria	Cold contact urticaria	Eliciting factor: cold air/water/wind
	Delayed pressure urticaria	Eliciting factor: vertical pressure (wheals arising with a 3–8 h latency)
	Heat contact urticaria	Eliciting factor: localized heat
	Solar urticaria	Eliciting factor: UV and/or visible light
	Urticaria factitia/dermographic urticaria	Eliciting factor: mechanical shearing forces (wheals arising after 1–5 min)
Other urticaria disorders	Vibratory urticaria/angioedema	Eliciting factor: vibratory forces, e.g. pneumatic hammer
	Aquagenic urticaria	Eliciting factor: water
	Cholinergic urticaria	Elicitation by increase of body temperature
	Contact urticaria	Elicitation by contact with urticariogenic substance
	Exercise-induced anaphylaxis/urticaria	Eliciting factor: physical exercise

more different subtypes of urticaria can coexist in any given patient. Table 1 presents a classification for clinical use. It is clear that there are some inconsistencies in this classification, e.g. physical urticarias are also chronic conditions but they are grouped separately because of the special nature of their eliciting physical factors, whereas in typical acute and chronic urticarias, wheals arise spontaneously without external physical stimuli.

Urticaria pigmentosa (cutaneous mastocytosis), urticarial vasculitis, familial cold urticaria and nonhistaminergic angioedema (e.g. hereditary or acquired angioedema) are no longer considered as subtypes of urticaria, but are listed in Table 2 for reference. Chronic urticaria or other subtypes of urticaria can also be features of several eponymous syndromes (Table 2).

Another important factor in classifying urticaria is disease activity. Where physical triggers are implicated an exact measurement of the intensity of the eliciting factor can be made, e.g. the temperature and duration of application in cold urticaria or pressure, and the duration of application until provocation of lesions in delayed pressure urticaria. For nonphysical acute and chronic urticaria, assessing disease activity is more complex. Several scoring systems have been proposed using scales from 0 to 3 or up to 10 points. Here, we propose a unified scoring system that would facilitate comparison of study results from different centres. This simple scoring system (Table 3) is based on the assessment of key urticaria

Table 2. Diseases related to urticaria for historical reasons and syndromes that include urticaria/angioedema

Diseases related to urticaria for historical reasons
Urticaria pigmentosa (mastocytosis)
Urticarial vasculitis
Familial cold urticaria (vasculitis)
Nonhistaminergic angioedema (e.g. HAE)
Syndromes that can be associated with urticaria/angioedema
Muckle-Wells syndrome
Schnitzler's syndrome
Gleich's syndrome
Well's syndrome

HAE, hereditary angioedema.

Table 3. Assessment of disease activity in urticaria patients

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 h)	Mild
2	Moderate (21–50 wheals/24 h)	Moderate
3	Intense (>50 wheals/24 h or large confluent areas of wheals)	Intense

Sum of score: 0–6.

symptoms (wheals and pruritus). It is also suitable for evaluation of disease activity by urticaria patients and their treating doctors.

As urticaria symptoms frequently change in intensity during the course of a day, overall disease activity is best measured by advising patients to document 24-h self-evaluation scores for several days. In addition, a single time point evaluation and/or sequential physical examinations by the treating doctor can help to make the patient's score more objective.

Other aspects that have received insufficient attention in the past are inter-patient and within-patient differences in the appearance of wheals before and after treatment. In general, larger wheals indicate disease that is more severe and more difficult to treat. The colour of the wheals may provide a useful clue. Histamine-induced wheals are of light colour, surrounded by a pink erythema due to dilatation of cutaneous vessels. In contrast, wheals of a dark red or violaceous colour may reflect intense vascular damage and leakage in association with wheal formation, as found in urticarial vasculitis. It would therefore be desirable to assess the size and colour of wheals in the scoring system, but as these parameters are difficult to quantify, they have not been included.

Possible mechanisms in urticaria

In the last two decades, many advances have been made in identifying causes of different types and subtypes of urticaria underlying the heterogeneity of the disease, e.g.

in chronic urticaria (reviewed in Ref. 6). Among others, chronic infections (e.g. *Helicobacter pylori*), nonallergic intolerance reactions to foods and autoreactivity functional autoantibodies directed against the immunoglobulin E (IgE) receptor have been described (7–14). However, there is considerable variation in the frequency of eliciting factors in the different studies. This may reflect differences in patient selection, emphasizing the need for a consensus on the classification of urticaria subtypes that will allow the comparison of results from different centres.

A number of attempts have been made to classify urticaria subtypes on the basis of underlying mechanisms. This is not routinely practised in the clinic and neither the panel nor the workshop participants thought that such a classification was useful because of the extensive overlap between different urticaria subtypes. To avoid confusion, we recommend that the classification outlined in Table 1 should be used for routine purposes.

Diagnosis of urticaria

Because of the heterogeneity of urticaria and its many subtypes, guidelines for diagnosis might start with a routine patient evaluation, which should comprise a thorough history and physical examination, and the ruling out of severe systemic disease by basic laboratory tests. Specific provocation and laboratory tests should be carried out on an individually on the basis of the suspected cause.

Of all the diagnostic procedures, the most important is to obtain a thorough history including all possible eliciting factors and significant aspects of the nature of the urticaria. Questions should be asked regarding the following items (15):

- 1 time of onset of disease;
- 2 frequency and duration of wheals;
- 3 diurnal variation;
- 4 shape, size and distribution of wheals;
- 5 associated angioedema;
- 6 associated subjective symptoms of lesion, e.g. itch, pain;
- 7 family history regarding urticaria, atopy;
- 8 previous or current allergies, infections, internal diseases, or other possible causes;
- 9 induction by physical agents or exercise;
- 10 use of drugs [nonsteroidal anti-inflammatory drugs (NSAIDs), injections, immunizations, hormones, laxatives, suppositories, ear and eye drops and alternative remedies];
- 11 food;
- 12 smoking habits;
- 13 type of work;
- 14 hobbies;
- 15 occurrence in relation to weekends, holidays and foreign travel;
- 16 surgical implantations;
- 17 reactions to insect stings;
- 18 relationship to the menstrual cycle;
- 19 response to therapy;
- 20 stress;
- 21 quality of life related to urticaria.

The second step is physical examination of the patient. This should include a test for dermatographism (e.g. antihistamine therapy should be discontinued for at least 2–3 days and immunosuppressive therapy for at least 1 week). Subsequent diagnostic steps will depend on the nature of the urticaria subtype, as summarized in Table 4.

Table 4. Recommended diagnostic tests in frequent urticaria subtypes

Group	Subgroup	Routine diagnostic tests	Extended diagnostic programme*
Spontaneous urticaria	Acute urticaria	None†	None†
	Chronic urticaria	Differential blood count and ESR/CRP‡, omission of suspected drugs (e.g. NSAID)	Test for (i) infectious diseases (e.g. <i>Helicobacter pylori</i>); (ii) type I allergy; (iii) autoantibodies; (iv) thyroid hormones; (v) physical tests; (vi) pseudoallergen-free diet for 3 weeks and tryptase, biopsy
Physical urticaria	Cold contact urticaria	Cold provocation and threshold test (ice cube, cold water, cold wind)	Differential blood count and ESR/CRP‡, cryoproteins rule out other diseases, especially infections
	Delayed pressure urticaria	Pressure test (0.2–1.5 kg/cm ² for 10 and 20 min)	None
	Heat contact urticaria	Heat provocation and threshold test (warm water)	None
	Solar urticaria	UV and visible light of different wave lengths	Rule out other light-induced dermatoses
	Dermatographic urticaria/urticaria factitia	Elicit dermatographism	Differential blood count, ESR/CRP
Other urticaria disorders	Aquagenic urticaria	Wet cloths at body temperature applied for 20 min	None
	Cholinergic urticaria	Exercise and hot bath provocation	None
	Contact urticaria	Prick/patch test read after 20 min	None
	Exercise-induced anaphylaxis/urticaria	According to history exercise test with/without food	None

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NSAID, nonsteroidal anti-inflammatory drugs.

*Depending on suspected cause.

†Unless strongly suggested by patient history, e.g. allergy.

‡As indication of severe systemic disease.

The panel strongly advises against intensive and costly general screening programmes for causes of urticaria. Type I allergy is a rare cause of chronic persistent urticaria but must be considered in chronic persistent urticaria, whereas pseudoallergic reactions to food or food additives may be more relevant for chronic continuous urticaria. In exercise-induced anaphylaxis both allergic and nonallergic reactions to food should be taken into account, especially type I allergy to wheat and gliadin as well as unspecific reactions to alcoholic beverages. Chronic persistent bacterial infections, e.g. with *H. pylori*, streptococci, staphylococci, or *Yersinia*, can trigger urticarial symptoms (12). The frequency and relevance of infectious diseases varies between different patient groups and in different regions. For example, hepatitis virus infections are a frequent cause for chronic urticaria in southern Europe but a rare cause in northern Europe. *Anisakis simplex*, a seafish nematode, may be an important cause of anaphylaxis in areas where uncooked fish is eaten frequently (16). The relevance of dental or ENT infections appears to vary between patient groups.

Currently, the only generally available test to screen for autoantibodies against the IgE receptor is the autologous serum skin test, a nonspecific screening test which evaluates the presence of serum histamine-releasing factors of any type, not just histamine-releasing auto-

antibodies. Both panel and audience advised that this test should be performed with utmost care since infections might be transmitted if, by mistake, patients were injected with someone else's serum. A more refined laboratory test evaluates the *in vitro* histamine release from basophils which is offered at special centres.

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