

Definition, Classification, and Routine Diagnosis of Urticaria: A Consensus Report¹

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Urticaria is a well-known disease entity; however, with an increasing understanding of the molecular mechanisms involved in its pathogenesis, there is also growing evidence for a heterogeneity of urticaria. Currently it is sometimes difficult to compare divergent data reported by different centers researching urticaria due to a lack of precisely described patient populations. A consensus definition and clas-

sification of the disease and its subtypes, taking into account new developments, are therefore needed. In addition, this consensus report provides a guideline for diagnostic procedures in different subtypes of urticaria. **Key words:** autologous serum/chronic urticaria/etiology/wheel. *Journal of Investigative Dermatology Symposium Proceedings* 6:123–127, 2001

This consensus report is the result of a panel discussion during the International Clinically Oriented ESDR Symposium "Urticaria 2000". The authors as members of the panel had prepared their suggestions regarding definition, classification, and routine diagnosis of urticaria in advance. These suggestions were then discussed in detail with the participants of the meeting using simple voting systems. The participation of more than 100 specialists in urticaria from over 15 countries ensured that this consensus includes any regional differences in viewpoint and hopefully provides a basis for improved comparison of future planned studies in the field of urticaria.

Urticaria was described as a distinct entity by Hippocrates, but many different subtypes have been recognized during the past century. With an increasing understanding of the molecular mechanisms involved in its pathogenesis, there is also growing evidence for a heterogeneity of urticaria. An updated definition and classification of urticaria, to include new developments, are therefore needed. These should facilitate the interpretation of divergent data from different centers regarding eliciting causes for subtypes of urticaria and their therapeutic responsiveness.

DEFINITIONS

Clinical appearance Urticaria is characterized by the rapid appearance of wheals, which may be accompanied by angioedema.

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; (iii) its fleeting nature,

with the skin returning to its normal appearance usually within 1–24 h.

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

Histologic aspects On histology, the classical fleeting wheal demonstrates edema of the epidermis and the upper and mid-dermis, with dilatation of the postcapillary venules and lymphatic vessels of the upper dermis. In angioedema similar changes primarily involve the lower dermis and the subcutis. Dependent on the duration of the wheals, there is always an upregulation of endothelial adhesion molecules, a mixed inflammatory perivascular infiltrate of variable intensity, consisting of neutrophils and/or eosinophils, macrophages, and T-helper lymphocytes (Haas *et al*, 1998). A mild to moderate increase of mast cell numbers has also been observed. In delayed pressure urticaria the infiltrate is located typically in the mid- to lower dermis (Barlow *et al*, 1994). In different subtypes of urticaria, alterations of adhesion molecules (Zuberbier *et al*, 1997) and cytokine expression is also seen in uninvolved skin (Hermes *et al*, 1999).

These recent findings underline the complex nature of the pathogenesis of urticaria, which has many features in addition to release of histamine from dermal mast cells. The changes are generally also seen in other diverse inflammatory reactions and are thus not specific or diagnostic. A search for more specific 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, in one patient two or more different subtypes of urticaria can coexist. **Table I** presents a classification for clinical use. As is evident, there are some inconsistencies in this classification, e.g., physical urticarias are also of a chronic nature. They are, nevertheless, grouped separately

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

	<u>duration</u>	<u>frequency</u>
a. spontaneous urticaria		
1. acute urticaria	< 6 wk	spontaneous wheals appearing most days
2. chronic urticaria	> 6 wk	spontaneous appearance of wheals
– chronic continuous urticaria	daily or on most days of the week	
– chronic recurrent urticaria	symptom free intervals ranging from days to weeks	
	<u>eliciting factor</u>	
b. physical urticaria		
1. dermatographic urticaria	mechanical shearing forces (wheals arising after 1–5 min)	
2. delayed pressure urticaria	vertical pressure (wheals arising with a 3–8 h latency)	
3. cold contact urticaria	cold air/water/wind	
4. heat contact urticaria	localized heat	
5. solar urticaria	UV and/or visible light	
6. vibratory urticaria/angioedema	vibratory forces, e.g., pneumatic hammer	
c. special types of urticaria		
1. cholinergic urticaria		
2. adrenergic urticaria		
3. contact urticaria (allergic or pseudoallergic)		
4. aquagenic urticaria		
d. different diseases related to urticaria for historical reasons		
4. urticaria pigmentosa (mastocytosis)		
5. urticarial vasculitis		
6. familial cold urticaria (a vasculitis)		

Table II. Assessment of disease intensity

Score ^a	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

^aSum of score: (0–6).

due to the special nature of their eliciting physical factors, whereas in acute and chronic urticaria wheals arise spontaneously without external physical stimuli. In addition, for historic reasons, some disease entities have been included under the heading “urticaria”, although they do not fulfil the strict definitions for wheals or angioedema, such as urticaria pigmentosa, urticarial vasculitis, and familial cold urticaria, where both reactions represent typical vasculitis.

Another important defining factor in urticaria is disease severity. In the different subtypes of physical urticaria an exact measurement of the intensity of the eliciting factor can be made, e.g., the temperature and time of application in cold urticaria or the pressure and time of application until provocation of lesions in delayed pressure urticaria. For acute and chronic urticaria assessing severity is more complex. In the past, different point scoring systems have been proposed ranging from 0 to 3 and up to 10. In order to improve comparison of study results from different centers a unified scoring system is required.

We propose a simple scoring system that is suitable for both the patient's daily evaluation and the doctor's evaluation at the time of the patient's visit (**Table II**). Due to the change in intensity during the day, a 24 h patient self-evaluation score represents probably the most exact parameter for assessing the overall intensity of the disease. In addition, a single time point evaluation by the treating

Table III. Possible mechanisms for urticaria

Mechanism	Examples
a. immunologic	
1. antigen-induced	drug allergy food allergy insect allergy
2. immunoglobulin-mediated; unknown antigen	some physical urticarias (cold, dermatographic, solar)
3. autoimmune	chronic idiopathic urticaria with IgE-receptor or thyroid autoantibodies, SLE, rheumatic fever
b. infectious	
1. viral diseases	hepatitis A or B, CMV, Coxsackie viruses
2. bacterial diseases	helicobacter pylori, streptococci
3. fungal infections	trichophyton, candida
4. parasites	giardia lamblia, entamoeba, trichinella
c. pseudoallergic	
1. complement mediated	heat urticaria hereditary angioedema reactions to blood products
2. unknown	NSAID, food
d. other	
1. histamine releasing chemicals	polycations codeine polymyxin B
2. internal diseases	tumors, sarcoidosis

physician, based primarily on visible symptoms at the time of the patient's visit, helps to make the patient score more objective. Due to diurnal rhythms in urticaria intensity, sequential physical examinations should be performed at the same time of day. Other aspects that have received insufficient attention in the past are interpatient and within-patient differences in the appearance of wheals before and after treatment. In general, larger wheals indicate a more severe and difficult to treat disease.

An important aspect is the color of the wheals. Histamine-induced wheals are of light color, surrounded by a pink erythema

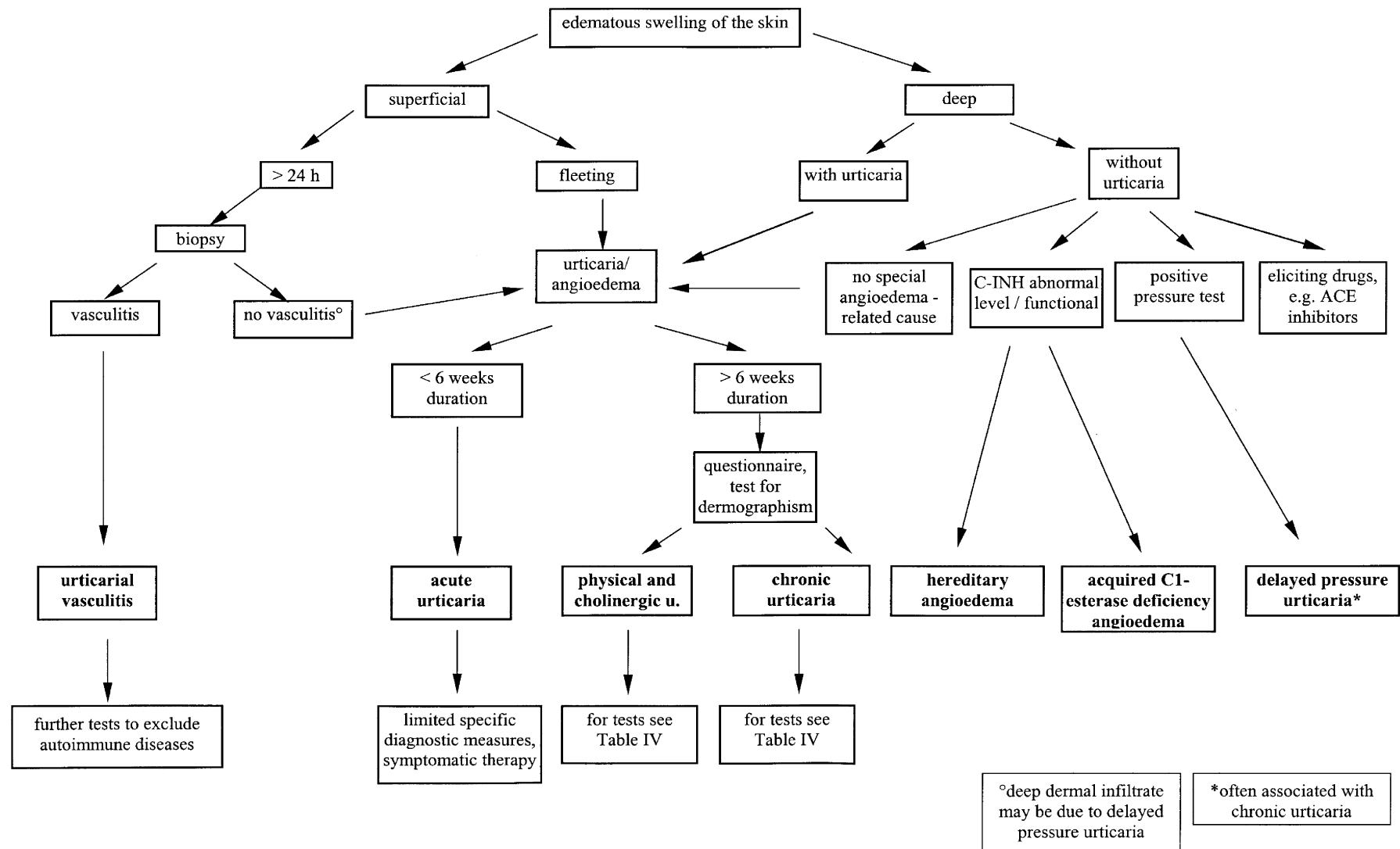


Figure 1. Flow sheet as an aide in the stepwise procedure for the diagnosis of urticaria.

Table IV. Standard diagnostic programme^a

Routine diagnostic tests	
a. acute urticaria	no routine diagnostic tests (unless strongly suggested by patient history)
b. chronic urticaria	differential blood count ESR (as indication of severe systemic disease) omission of suspected drugs, e.g. NSAID possibly: autologous serum skin test, test for helicobacter, gastroscopy, ANA, stool for worm eggs/parasites, skin tests, specific IgE, thyroid hormones and autoantibodies pseudoallergen-free diet for 3 weeks
c. physical urticaria	
1. dermographic urticaria	elicit dermatographism differential blood count and ESR (as indication of severe systemic disease)
2. delayed pressure urticaria	pressure test (0.2–0.4 kg per cm ² for 10 and 20 min)
3. cold urticaria	cold provocation test (ice cube, cold water), use different temperatures to identify threshold possibly: exposure to cold wind (ventilator), differential, ESR, cryoglobulins
4. heat contact urticaria	warm arm bath (42°C; vary temperature to detect threshold)
5. solar urticaria	UV and visible light of different wave lengths
d. special types of urticaria	exercise or hot bath according to patient history
cholinergic urticaria	
e. other diseases	biopsy, differential, ESR, ANA, biochemistry urine test
urticarial vasculitis	

^aThis table gives a selection of frequent urticaria subtypes to be considered in diagnosis or differential diagnosis.

due to dilatation of cutaneous vessels. If wheals are of a dark red or violaceous color, as, for example, in urticarial vasculitis, this indicates intense vascular damage and leakage in association with wheal formation. It would also be desirable to assess the size and color of wheals in the scoring system, but as these parameters are difficult to quantify they are not included.

POSSIBLE MECHANISMS IN URTICARIA

In the last two decades many advances have been made to identify causes of different types and subtypes of urticaria underlining the heterogeneity of the disease even in one subtype, e.g., chronic urticaria. Among others, infections, pseudoallergy against food, and IgE receptor autoantibodies have been repeatedly described (Juhlin, 1981; Hide *et al*, 1993; Zuberbier *et al*, 1995; Fiebiger *et al*, 1998; Greaves, 2000); however, in different studies there is considerable variation in the frequency of eliciting factors. One cause for this may be due to differences in patient selection, underlining the necessity for a consensus in the precise patient selection data to enable comparison of results between different patient groups to be made.

Attempts to classify urticaria on the basis of underlying mechanisms have been made in the past. This is not practised in the clinic and the panel as well as the participants decided not to use such a classification, due to many overlaps between urticaria types. To avoid confusion only the classification outlined in **Table I** should be used for routine purposes; however, to increase awareness of the possible mechanisms involved and to clarify the largely idiopathic forms of urticaria, a list of possible pathomechanisms with examples is given in **Table III**. The relevance of the items listed is variable and depends on the subtype of urticaria.

DIAGNOSIS OF URTICARIA

Due to the heterogeneity of the disease and its many subtypes, guidelines for diagnosis can only cover a routine programme, including a thorough history and physical examination as well as specific provocation and laboratory tests on the basis of the suspected cause.

Of all diagnostic procedures, a thorough history including all possible eliciting factors and significant aspects as to the nature of the urticaria is of paramount importance. The questions that should be asked include the following items (Henz *et al*, 1998):

- (1) time of onset of disease;

- (2) frequency and duration of whealing;
- (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 currently existing allergies, infections, internal diseases, or other possible causes;
- (9) induction by physical agents or exercise;
- (10) use of drugs (NSAID, 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 the physical examination of the patient. This should include a test for dermatographism when the patient has ceased antihistamine therapy for at least 2 d. The subsequent diagnostic steps depend on the nature of the urticaria subtype and are summarized in the flow sheet (**Fig 1**).

The panel strongly advises against intense and costly general screening programmes for urticaria. Standardized diagnostic tests for a number of urticaria subtypes are summarized in **Table IV**. Additional tests should be reserved for selected patients. Type I allergy is a rare cause in chronic continuous urticaria but must be considered in chronic intermittent urticaria, whereas pseudoallergy to food or food additives may be more important for chronic continuous urticaria. The frequency and relevance of infectious diseases varies between different patient groups and in different regions. For example, the participants pointed out that hepatitis virus infections are a frequent cause for chronic urticaria in southern Europe but a rare cause in northern Europe. The necessity to investigate 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. Both the panel and the participants advised that the test should be performed with the utmost care, as infections (e.g., HIV, hepatitis) could be transmitted particularly if, by mistake, patients were not injected with their own serum.

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