

Position paper

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

This guideline, together with its sister guideline on the management of urticaria [Zuberbier T, Asero R, Bindslev-Jensen C, Canonica GW, Church MK, Giménez-Arnau AM et al. EAACI/GA²LEN/EDF/WAO Guideline: Management of urticaria. *Allergy*, 2009; **64**:1427–1443] is the result of a consensus reached during a panel discussion at the 3rd International Consensus Meeting on Urticaria, *Urticaria 2008*, a joint initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the EU-funded network of excellence, the Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF) and the World Allergy Organization (WAO). Urticaria is a frequent disease. The life-time prevalence for any subtype of urticaria is approximately 20%. Chronic spontaneous urticaria and other chronic forms of urticaria do not only cause a decrease in quality of life, but also affect performance at work and school and, as such, are members of the group of severe allergic diseases. This guideline covers the definition and classification of urticaria, taking into account the recent progress in identifying its causes, eliciting factors, and pathomechanisms. In addition, it outlines evidence-based diagnostic approaches for different subtypes of urticaria. The correct management of urticaria, which is of paramount importance for patients, is very complex and is consequently covered in a separate guideline developed during the same consensus meeting. This guideline was acknowledged and accepted by the European Union of Medical Specialists (UEMS).

T. Zuberbier¹, R. Asero², C. Bindslev-Jensen³, G. Walter Canonica⁴, M. K. Church¹, A. Giménez-Arnau⁵, C. E. H. Grattan⁶, A. Kapp⁷, H. F. Merk⁸, B. Rogala⁹, S. Saini¹⁰, M. Sánchez-Borges¹¹, P. Schmid-Grendelmeier¹², H. Schünemann¹³, P. Staubach¹⁴, G. A. Vena¹⁵, B. Wedi⁷, M. Maurer¹

¹Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Germany; ²Ambulatorio di Allergologia, Clinica San Carlo, Paderno Dugnano (MI), Italy; ³Allergy Centre, Department of Dermatology, Odense University Hospital, Denmark; ⁴Allergy and Respiratory Diseases, DIMI – University of Genoa, Genoa, Italy; ⁵Department of Dermatology, Hospital del Mar, IMAS, Universitat Autònoma of Barcelona, Spain; ⁶Dermatology Centre, Norfolk & Norwich University Hospital, Norwich, UK; ⁷Department of Dermatology and Allergology, Hannover Medical University, Germany; ⁸Department of Dermatology, University Hospital RWTH Aachen, Germany; ⁹Clinical Department of Internal Diseases, Allergology and Clinical Immunology, Medical University of Silesia, Poland; ¹⁰Department of Medicine, Johns Hopkins University, Baltimore, MD, USA; ¹¹Allergy and Immunology Department, Centro Medico-Docente La Trinidad, Caracas, Venezuela; ¹²Allergy Unit, Department of Dermatology, University Hospital, Zurich, Switzerland; ¹³Department of Clinical Epidemiology & Biostatistics, Hamilton, Canada; ¹⁴Department of Dermatology, Johannes Gutenberg-University, Mainz, Germany; ¹⁵Unit of Dermatology, University of Bari, Bari, Italy

Key words: consensus; diagnosis; guideline; urticaria; wheal

Torsten Zuberbier
Charité – Universitätsmedizin Berlin
Allergie-Centrum-Charité
Charitéplatz 1
D-10117 Berlin
Germany

Accepted for publication 3 July 2002

This guideline is the result of a panel discussion during the 3rd International Meeting on Urticaria *Urticaria 2008*, a joint initiative of the EAACI Dermatology Section, GA²LEN, EDF and WAO.

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.

Methods

As members of the panel, the authors had prepared in advance their suggestions regarding the definition, classification, and routine diagnosis of urticaria (Table 1). The draft of the guideline took into account all available evidence in the literature (including Medline and Embase searches and hand searches of abstracts at international allergy congresses in 2004–2008) and was based on the existing consensus papers of the first and second symposium in 2000 and 2004 (1, 2). These suggestions were then discussed in detail among the panel and the participants of the meeting and a consensus achieved using a simple voting system where appropriate. The participation of more than 200 specialists in urticaria from 33 countries ensured that this consensus included European and global regional differences in viewpoint and provided a basis for improved comparison of future studies in the field of urticaria.

Table 1. Box of recommendations and suggestions for the diagnosis of urticaria

- We recommend adhering to the definitions of urticaria types and subtypes provided by these guidelines in order to avoid misunderstandings both in patient care as well as in publications.
- We recommend following the classification of urticaria as outlined in Table 2 in clinical trials, publications and routine daily practice.
- We suggest using the urticaria activity score (UAS) in routine daily practice to assess disease severity and monitor success of treatment in patients with spontaneous urticaria.
- Furthermore we strongly recommend the use of this validated score in clinical trials to allow comparison with others.
- We recommend a stepwise diagnostic approach as outlined in Table 5.
- We suggest using the same procedure in children.

Definition

Urticaria is a heterogeneous group of diseases. All types and subtypes of urticaria share a common distinctive skin reaction pattern, i.e. the development of urticarial skin lesions and/or angioedema. Urticaria needs to be differentiated from other medical conditions where wheals can occur as a symptom, e.g. skin prick test or acute anaphylaxis without symptoms in daily life.

Clinical appearance

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

A wheal consists of three typical features:

1. a central swelling of variable size, almost invariably surrounded by a reflex erythema
2. associated itching or, sometimes, burning sensation
3. a fleeting nature, with the skin returning to its normal appearance, usually within 1–24 h

Angioedema is characterized by:

1. a sudden, pronounced swelling of the lower dermis and subcutis
2. sometimes pain rather than itching
3. frequent involvement below mucous membranes
4. resolution that is slower than for wheals and can take up to 72 h

Histological aspects

On histology, the classical fleeting wheal demonstrates edema 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

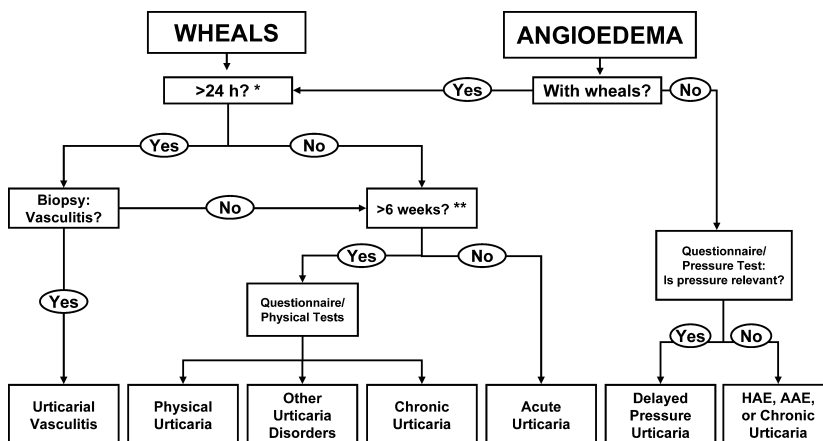


Figure 1. Differential diagnosis of urticarial symptoms. HAE, hereditary angioedema; AAE, acquired angioedema with C1 Esterase inhibitor deficiency; SA, spontaneous angioedema as manifestation of chronic urticaria with only deep swellings but no superficial wheals. *Duration of individual wheals; **duration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

of endothelial adhesion molecules and a mixed inflammatory perivascular infiltrate of variable intensity, consisting of neutrophils and/or eosinophils, macrophages, and T-cells (3). A mild to moderate increase of mast cell numbers has also been reported by some authors. In delayed pressure urticaria, the infiltrate is typically located in the mid to lower dermis. 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 (6, 7).

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 more different subtypes of urticaria can coexist in any given patient. Table 2 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 due to the special nature of their eliciting physical factors, whereas in typical acute and chronic spontaneous urticarias wheals arise spontaneously without external physical stimuli. However, it should be noted to avoid confusion that the commonly used abbreviation for chronic urticaria remains chronic urticaria even if the full term is

chronic spontaneous urticaria. This expression is chosen only for classification purposes.

Urticaria pigmentosa (cutaneous mastocytosis), urticarial vasculitis, familial cold urticaria and nonhistaminergic angioedema (e.g. hereditary or acquired C1 esterase inhibitor deficiency) are no longer considered as subtypes of urticaria, due to their distinctly different pathomechanisms, but are listed in Table 3 for reference. Wheals are features of several eponymous syndromes (Table 3).

Another important factor in classifying urticaria is disease activity. In physical urticaria and in cholinergic urticaria, as well as exercise-induced urticaria/anaphylaxis, the threshold of the eliciting factor(s) should be determined, e.g. critical temperature and stimulation time thresholds for cold provocation in cold urticaria. These thresholds allow both patients and treating physicians to evaluate disease activity and response to treatment. For acute and chronic spontaneous urticaria, assessing disease activity is more complex. Several scoring systems have been proposed using scales from 0–3 or up to 10 points. A unified and simple scoring system, the urticaria activity score (UAS), was proposed in the last version of the guidelines. Use of the UAS facilitates comparison of study results from different centres. The UAS (Table 4) is based on the assessment of key urticaria symptoms (wheals and pruritus). It is suitable for the evaluation of disease activity by urticaria patients and their treating physicians. Furthermore, this scoring system has been validated (8). As urticaria symptoms frequently change in intensity, overall disease activity is best measured by advising patients to document 24-h self-evaluation scores for several days. The UAS, i.e. the sum score of 7 consecutive days, should be used in routine clinical practice to determine disease activity and response to treatment of chronic urticaria patients. As CU-Q₂oL, a disease specific questionnaire

Table 2. Classification of urticaria subtypes (presenting with wheals and/or angioedema)

Types	Subtypes	Definition
Spontaneous urticaria	Acute spontaneous urticaria	Spontaneous wheals and/or angioedema < 6 weeks
	Chronic spontaneous urticaria	Spontaneous wheals and/or angioedema > 6 weeks
Physical urticaria	Cold contact urticaria	Eliciting factor: cold objects/air/fluids/wind
	Delayed pressure urticaria	Eliciting factor: vertical pressure (wheals arising with a 3–12 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)
	Vibratory urticaria/angioedema	Eliciting factor: vibratory forces, e.g. pneumatic hammer
Other urticaria types	Aquagenic urticaria	Eliciting factor: water
	Cholinergic urticaria	Elicitation by increase of body core temperature due to physical exercises, spicy food
	Contact urticaria	Elicitation by contact with urticariogenic substance
	Exercise induced anaphylaxis/urticaria	Eliciting factor: physical exercise

Table 3. 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 (Urticaria-deafness-amyloidosis), sensorineural deafness, recurrent urticaria (hives), fevers, arthritis	
Schnitzler's syndrome monoclonal gammopathy, recurrent fever, arthritis	
Gleich's syndrome (episodic angioedema with eosinophilia), IgM gammopathy, eosinophilia	
Well's syndrome (Eosinophilic cellulitis), granulomatous dermatitis with eosinophilia	

Table 4. Assessment of disease activity in urticaria patients

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 h)	Mild (present but not annoying or troublesome)
2	Moderate(20-50 wheals/24 h)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (>50 wheals/24 h or large confluent areas of wheals)	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)

Sum of score: 0–6.

for assessing quality of life in patients with chronic spontaneous urticaria is becoming available and validated in several languages; this instrument should be used to assess disease activity in chronic urticaria patients (9–12).

Possible mechanisms in urticaria

In the last two decades, many advances have been made in identifying causes of different types and subtypes of urticaria, e.g. in chronic spontaneous urticaria (reviewed in (13) and (14)). Among others, acute or chronic infections (e.g. *Anisakis simplex* or *Helicobacter pylori*), nonallergic hypersensitivity reactions to foods and drugs (pseudoallergic), and autoreactivity including autoimmunity mediated by functional autoantibodies directed against the IgE receptor have been described (15–23). The concept of autoimmune urticaria is increasingly being recognized but has still to be defined. However, there are considerable variations in the frequency of underlying causes 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.

Diagnosis of urticaria

Chronic spontaneous urticaria is a disease with a high burden for patients (11) and high direct and indirect healthcare costs (24) with large socio-economic implications due to a reduction in performance of 20–30%. Due to the heterogeneity of urticaria and its many subtypes, 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, should be performed first. Specific provocation, e.g. with a pseudoallergen rich diet, and laboratory tests are helpful for the identification of underlying causes of chronic spontaneous urticaria, whereas this is very unlikely in physical and other inducible urticarias. Extended diagnostic procedures in patients with the latter two types of urticaria should therefore only be carried out on an individual basis, i.e. in patients where the routine patient evaluation has uncovered a specific potential cause of urticaria. Extended diagnostics aimed at the identification of underlying causes should be performed in patients that suffer from longstanding, severe and/or persistent urticaria symptoms (Table 5).

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 (17):

1. Time of onset of disease
2. Frequency and duration of wheals
3. Diurnal variation
4. Occurrence in relation to weekends, holidays, and foreign travel
5. Shape, size, and distribution of wheals
6. Associated angioedema
7. Associated subjective symptoms of lesion, e.g. itch, pain
8. Family and personal history regarding urticaria, atopy
9. Previous or current allergies, infections, internal diseases, or other possible causes
10. Psychosomatic and psychiatric diseases
11. Surgical implantations and events during surgery
12. Gastric/intestinal problems (stool, flatulence)
13. Induction by physical agents or exercise
14. Use of drugs (NSAIDs, injections, immunizations, hormones, laxatives, suppositories, ear and eye drops, and alternative remedies)
15. Observed correlation to food
16. Relationship to the menstrual cycle
17. Smoking habits
18. Type of work
19. Hobbies
20. Stress (eustress and distress)
21. Quality of life related to urticaria and emotional impact
22. Previous therapy and response to therapy

Table 5. Recommended diagnostic tests in frequent urticaria subtypes

Types	Subtypes	Routine diagnostic tests (recommended)	Extended diagnostic programme* (suggested) For identification of eliciting factors and for ruling out possible differential diagnoses if indicated
Spontaneous urticaria	Acute spontaneous urticaria	None	None†
	Chronic spontaneous urticaria	Differential blood count and ESR or CRP omission of suspected drugs (e.g. NSAID)	Test for (i) infectious diseases (e.g. <i>Helicobacter pylori</i>); (ii) type I allergy; (iii) functional autoantibodies; (iv) thyroid hormones and autoantibodies; (v) skin tests including physical tests; (vi) pseudoallergen-free diet for 3 weeks and tryptase‡, (vii) autologous serum skin test, lesional skin 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
	Dermographic urticaria/ urticaria factitia	Elicit dermatographism	Differential blood count, ESR/CRP
Other urticaria types	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	According to history exercise	None
	anaphylaxis/urticaria	test with/without food but not after a hot bath	

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 second step is the physical examination of the patient. This should include a test for dermatographism where indicated by history (NB: antihistamine therapy should be discontinued for at least 2–3 days). Subsequent diagnostic steps will depend on the nature of the urticaria subtype, as summarized in Table 5.

Intensive and costly general screening programmes for causes of urticaria are strongly advised against. Type I allergy is a rare cause of chronic spontaneous urticaria in patients who present with daily or almost daily symptoms, but must be considered in chronic spontaneous urticaria patients with intermittent symptoms. In contrast, nonallergic hypersensitivity reactions to food or food additives may be more relevant for chronic spontaneous urticaria with persistent symptoms. Diagnosis should be based on an easy-to-follow diet protocol. Food challenge test for type I allergy should be preceded by an appropriate elimination diet. In exercise-induced urticaria/anaphylaxis both allergic and nonallergic hypersensitivity reactions to food should be taken into account, especially type I allergy to wheat and gliadin as well as nonspecific reactions to alcoholic beverages. Chronic persistent bacterial, viral, parasitic, or fungal infections, e.g. with *H. pylori*, *streptococci*, *staphylococci*, *yersinia*,

Giardia lamblia, *mycoplasma pneumonia*, *hepatitis virus*, *norovirus*, *parvovirus B19*, *anisakis simplex*, *entamoeba* spp, *blastocystis* spp, have been suspected to trigger urticarial symptoms in patients with chronic spontaneous urticaria. The frequency and relevance of infectious diseases varies between different patient groups and different geographical regions. For example, *Anisakis simplex*, a sea fish nematode, has been discussed as possible cause of recurrent acute spontaneous urticaria in areas of the world where uncooked fish is eaten frequently (25). The relevance of dental or ENT infections appears to vary between patient groups. Altogether more research is needed for in order to make definitive recommendations regarding the role of infection in urticaria. In contrast to previous recommendations to screen for malignancies in the diagnosis of chronic spontaneous urticaria, this is no longer suggested since there is no evidence available for a correlation of urticaria with neoplastic diseases.

Currently, the only generally available test to screen for autoantibodies against either IgE or the high affinity IgE receptor is the Autologous Serum Skin Test (ASST), a nonspecific screening test which evaluates the presence of serum histamine-releasing factors of any type, not just

histamine-releasing autoantibodies. General experience, including that of the panel, is that healthy controls and patients without chronic spontaneous urticaria do not have positive ASST responses as defined by an inflammatory red wheal response (26–35). In contrast to most previously published studies, some studies have demonstrated a relatively high prevalence of positive ASST reactivity in 30–50% of adult patients with allergic or nonallergic respiratory symptoms, reaching up to 80% in childhood populations (36–40). In two of these studies, 40–45% of healthy individuals also had a positive ASST although the criteria used to define positivity were adopted from those that had been validated only for chronic urticaria. The meaning of these discrepancies is unclear.

The ASST 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. The subject is further elucidated in a separate EAACI/GA²LEN position paper (41).

In physical urticaria the routine diagnosis is mainly aimed at the identification of the subtype by the appropriate physical stimulation tests and to the determination of trigger thresholds. The latter is important as it allows for assessing disease severity and response to treatment. For most types of physical urticaria no validated tools for provocation testing exist. Exceptions include cold urticaria, where a peltier element-based provocation device (TempTest®) is available (42, 43), and symptomatic dermographism urticaria facticia, for which a dermographometer has been developed (44). In other physical urticarias or cholinergic urticaria, graded provocation tests with office-based methods, e.g. ergometer provocation in cholinergic urticaria, should be standardized in the single practice setting to allow comparison of disease activity at different time points in the same patient.

In some subjects with active chronic spontaneous urticaria, several groups have noted blood basopenia and that blood basophils exhibit suppressed IgE receptor-mediated histamine release to anti-IgE. Blood basophils are detected in skin lesions and in nonlesional skin of chronic spontaneous urticaria patients. Chronic spontaneous urticaria remission is associated with increases in blood basophil numbers and IgE receptor triggered histamine response (45, 46). This finding, however, needs to be examined in future research and currently does not give lead to diagnostic recommendations. However, it should be noted that a low basophil blood count should not result in further diagnostic procedures.

Diagnosis in children

Urticaria can occur in all age groups. The underlying causes of chronic urticaria appear not to be different between children and adults (47) except possibly in infants (48). However, there appear to be differences

in the frequency of some of the underlying causes (49). In general, further epidemiological studies in children are needed. However, it is becoming apparent that the differences between the underlying causes of urticaria in children and adults are only small indicating that the diagnostic approach should, therefore, be the same as in adults (50, 51).

Need for further research

The panel and participants identified several areas which need further research.

These include but are not limited to

- epidemiology of urticaria
- the socio-economic consequences
- identification of mast cell basophil activating factors
- identifying new histological markers
- standardized procedures for testing physical urticaria
- standardized procedures for testing serum autoreactivity in chronic spontaneous urticaria
- determination of minimal important differences for instruments in quantifying a relevant response (e.g. UAS, CU-Q₂oL)
- clarification of the role of coagulation/coagulation factors in chronic spontaneous urticaria
- how to score angioedema reliably
- characterization of the relevance of nickel and food as possible triggering factor in chronic spontaneous urticaria

Acknowledgments

This guideline was generated in cooperation with the German Urticaria Patient Project "Urticaria Network e.V. (UNEV)" (Panel Delegate: Petra Staubach, Germany), the German Allergy and Asthma Union (DAAB) (Panel Delegate: Ingrid Voigtman, Germany), and the WAO and European Federation of Allergy and Airways Diseases Patients Association (EFA). The Global Allergy and Asthma European Network (GA²LEN), contract Number FOOD-CT-2004-506378, and the EAACI Dermatology section provided institutional and logistic support. We also wish to thank the European Centre for Allergy Research Foundation (ECARF) for organizing and financing the symposium and the publication of this guideline. ECARF is a nonprofit foundation administered by the Stifterverband für die Deutsche Wissenschaft (Donors' Association for the Promotion of the German Sciences and Humanities) with its office at the Department of Dermatology and Allergy at the Charité – Universitätsmedizin Berlin (see <http://www.ecarf.org>). ECARF is funded mainly by private donations. Other partners and sponsors of ECARF are REWE (a German supermarket chain) and Henkel (internationally aligned German-based company for Laundry & Home Care, Cosmetics/Toiletries and Adhesive Technologies). ECARF does not receive funding from pharmaceutical, weapon or tobacco industry. The authors would like to thank Allen Kaplan, National Allergy, Asthma, and Urticaria Centers of Charleston, Charleston, SC, USA, for his contribution in reviewing the article and offering very constructive

comments as well as Martin Metz and Markus Magerl, Department of Dermatology and Allergy, Charité - Universitätsmedizin Berlin, Germany, for their efficient organization of the consensus meeting and their profound contribution during the critical discussion of both guidelines. Furthermore, the authors especially

would like to thank all physicians and specialists (see Appendix) for their great cooperation and contribution on diagnosis and management of urticaria in the democratic process and discussion within the 3rd International Consensus Meeting on Urticaria, *Urticaria 2008*.

References

- Zuberbier T, Greaves MW, Juhlin L, Kobza-Black A, Maurer D, Stingl G et al. Definition, classification, and routine diagnosis of urticaria: a consensus report. *J Invest Dermatol Symp Proc* 2001;**6**:123–127.
- Zuberbier T, Bindslev-Jensen C, Canonica W, Grattan CE, Greaves MW, Henz BM et al. EAACI/GA2LEN/EDF guideline: definition, classification and diagnosis of urticaria. *Allergy* 2006;**61**:316–320.
- Haas N, Schadendorf D, Henz BM. Differential endothelial adhesion molecule expression in early and late whealing reactions. *Int Arch Allergy Immunol* 1998;**115**:210–214.
- Zuberbier T, Schadendorf D, Haas N, Hartmann K, Henz BM. Enhanced P-selectin expression in chronic and dermatographic urticaria. *Int Arch Allergy Immunol* 1997;**114**:86–89.
- Hermes B, Prochazka AK, Haas N, Jurgovsky K, Sticherling M, Henz BM. Upregulation of TNF-alpha and IL-3 expression in lesional and uninvolved skin in different types of urticaria. *J Allergy Clin Immunol* 1999;**103**:307–314.
- Greaves MW. Chronic urticaria. *N Engl J Med* 1995;**332**:1767–1772.
- Kaplan AP. Clinical practice. Chronic urticaria and angioedema. *N Engl J Med* 2002;**346**:175–179.
- Mlynek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M. How to assess disease activity in patients with chronic urticaria? *Allergy* 2008;**63**:777–780.
- Baiardini I, Giardini A, Pasquali M, Dignetti P, Guerra L, Specchia C et al. Quality of life and patients' satisfaction in chronic urticaria and respiratory allergy. *Allergy* 2003;**58**:621–623.
- Mlynek A, Magerl M, Hanna M, Lhachimi S, Baiardini I, Canonica G et al. The German version of the chronic urticaria quality-of-life- questionnaire (CU-Q2oL): Validation and initial clinical findings. *Allergy* 2009;**64**:927–936.
- Maurer M, Ortonne JP, Zuberbier T. Chronic urticaria: an internet survey of health behaviours, symptom patterns and treatment needs in European adult patients. *Br J Dermatol* 2009;**160**:633–641.
- Staubach P, Eckhardt-Henn A, Dechene M, Vonend A, Metz M, Magerl M et al. Quality of life in patients with chronic urticaria is differentially impaired and determined by psychiatric comorbidity. *Br J Dermatol* 2006;**154**:294–298.
- Zuberbier T, Maurer M. Urticaria: current opinions about etiology, diagnosis and therapy. *Acta Derm Venereol* 2007;**87**:196–205.
- Magerl M, Altrichter S, Boodstein N, Güzlebay O, Keßler B, Krause K et al. Urticaria - classification and strategies for diagnosis and treatment. *CME Dermatol* 2008;**3**:2–18.
- Daschner A, Pascual CY. Anisakis simplex: sensitization and clinical allergy. *Curr Opin Allergy Clin Immunol* 2005;**5**:281–285.
- Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. *Br J Dermatol* 1981;**104**:369–381.
- Zuberbier T, Chantraine-Hess S, Hartmann K, Czarnetzki BM. Pseudo-allergen-free diet in the treatment of chronic urticaria. A prospective study. *Acta Derm Venereol* 1995;**75**:484–487.
- Hide M, Francis DM, Grattan CE, Hakimi J, Kochan JP, Greaves MW. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med* 1993;**328**:1599–1604.
- Fiebiger E, Hammerschmid F, Stingl G, Maurer D. Anti-FcεpsilonRIalpha autoantibodies in autoimmune-mediated disorders. Identification of a structure-function relationship. *J Clin Invest* 1998;**101**:243–251.
- Buhner S, Reese I, Kuehl F, Lochs H, Zuberbier T. Pseudoallergic reactions in chronic urticaria are associated with altered gastroduodenal permeability. *Allergy* 2004;**59**:1118–1123.
- Wedi B, Raap U, Kapp A. Chronic urticaria and infections. *Curr Opin Allergy Clin Immunol* 2004;**4**:387–396.
- Wedi B, Kapp A. *Helicobacter pylori* infection in skin diseases: a critical appraisal. *Am J Clin Dermatol* 2002;**3**:273–282.
- Wedi B, Wagner S, Werfel T, Manns MP, Kapp A. Prevalence of *Helicobacter pylori*-associated gastritis in chronic urticaria. *Int Arch Allergy Immunol* 1998;**116**:288–294.
- DeLong LK, Culler SD, Saini SS, Beck LA, Chen SC. Annual direct and indirect health care costs of chronic idiopathic urticaria: a cost analysis of 50 nonimmunosuppressed patients. *Arch Dermatol* 2008;**144**:35–39.
- Foti C, Nettis E, Cassano N, Di Mundo I, Vena GA. Acute allergic reactions to *Anisakis simplex* after ingestion of anchovies. *Acta Derm Venereol* 2002;**82**:121–123.
- Grattan CE, Wallington TB, Warin RP, Kennedy CT, Bradfield JW. A serological mediator in chronic idiopathic urticaria – a clinical, immunological and histological evaluation. *Br J Dermatol* 1986;**114**:583–590.
- Niimi N, Francis DM, Kermani F, O'Donnell BF, Hide M, Kobza-Black A et al. Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. *J Invest Dermatol* 1996;**106**:1001–1006.
- Fagiolo U, Cancian M, Bertollo L, Peserico A, Amadori A. Inhibitory effect of heparin on skin reactivity to autologous serum in chronic idiopathic urticaria. *J Allergy Clin Immunol* 1999;**103**:1143–1147.
- Sabroe RA, Grattan CE, Francis DM, Barr RM, Kobza Black A, Greaves MW. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol* 1999;**140**:446–452.
- Asero R, Tedeschi A, Lorini M, Salimbeni R, Zanoletti T, Miadonna A. Chronic urticaria: novel clinical and serological aspects. *Clin Exp Allergy* 2001;**31**:1105–1110.
- Asero R, Tedeschi A, Lorini M. Auto-reactivity is highly prevalent in patients with multiple intolerances to NSAIDs. *Ann Allergy Asthma Immunol* 2002;**88**:468–472.

32. Confino-Cohen R, Aharoni D, Goldberg A, Gurevitch I, Buchs A, Weiss M et al. Evidence for aberrant regulation of the p21Ras pathway in PBMCs of patients with chronic idiopathic urticaria. *J Allergy Clin Immunol* 2002;**109**:349–356.
33. Asero R, Tedeschi A, Lorini M, Caldironi G, Barocci F. Sera from patients with multiple drug allergy syndrome contain circulating histamine-releasing factors. *Int Arch Allergy Immunol* 2003;**131**:195–200.
34. Metz M, Gimenez-Arnau A, Borzova E, Grattan CE, Magerl M, Maurer M. Frequency and clinical implications of skin autoreactivity to serum versus plasma in patients with chronic urticaria. *J Allergy Clin Immunol* 2009;**123**:705–706.
35. Bunselmeyer B, Laubach HJ, Schiller M, Stanke M, Luger TA, Brehler R. Incremental build-up food challenge – a new diagnostic approach to evaluate pseudoallergic reactions in chronic urticaria: a pilot study: stepwise food challenge in chronic urticaria. *Clin Exp Allergy* 2009;**39**:116–126.
36. Mari A. Allergy-like asthma and rhinitis. A cross-sectional survey of a respiratory cohort and a diagnostic approach using the autologous serum skin test. *Int Arch Allergy Immunol* 2004;**133**:29–39.
37. Guttman-Yassky E, Bergman R, Maor C, Mamorsky M, Pollack S, Shahar E. The autologous serum skin test in a cohort of chronic idiopathic urticaria patients compared to respiratory allergy patients and healthy individuals. *J Eur Acad Dermatol Venereol* 2007;**21**:35–39.
38. Jang AS, Park JS, Lee JH, Park SW, Kim DJ, Park CS. Autologous serum skin test for autoantibodies is associated with airway hyperresponsiveness in patients with asthma. *Respiration* 2007;**74**:293–296.
39. Comi AL, Tedeschi A, Lorini M, Miadonna A. Novel clinical and serological aspects in non-allergic asthma. *Respir Med* 2007;**101**:2526–2533.
40. Tedeschi A, Comi AL, Lorini M, Tosini C, Miadonna A. Autologous serum skin test reactivity in patients with non-allergic asthma. *Clin Exp Allergy* 2005;**35**:849–853.
41. Konstantinou GN, Asero R, Maurer M, Sabroe RA, Schmid-Grendelmeier P, Grattan CE. EAACI/GA²LEN Position Paper: the autologous serum skin test in urticaria: literature review and consensus panel recommendations. *Allergy* 2009;**64**:1256–1268.
42. Siebenhaar F, Staubach P, Metz M, Magerl M, Jung J, Maurer M. Peltier effect-based temperature challenge: an improved method for diagnosing cold urticaria. *J Allergy Clin Immunol* 2004;**114**:1224–1225.
43. Mlynek A, Magerl M, Siebenhaar F, Weller K, Viera dos Santos R, Zuberbier T et al. Results and relevance of critical temperature threshold 1 testing in patients with acquired cold urticaria. *Br J Dermatol* 2009; **161**:472–474.
44. Lawlor F, Black AK. Delayed pressure urticaria. *Immunol Allergy Clin North Am* 2004;**24**:247–258, vi–vii.
45. Grattan CE, Dawn G, Gibbs S, Francis DM. Blood basophil numbers in chronic ordinary urticaria and healthy controls: diurnal variation, influence of loratadine and prednisolone and relationship to disease activity. *Clin Exp Allergy* 2003;**33**:337–341.
46. Eckman JA, Hamilton RG, Gober LM, Sterba PM, Saini SS. Basophil phenotypes in chronic idiopathic urticaria in relation to disease activity and autoantibodies. *J Invest Dermatol* 2008;**128**:1956–1963.
47. Ehlers I, Niggemann B, Binder C, Zuberbier T. Role of nonallergic hypersensitivity reactions in children with chronic urticaria. *Allergy* 1998;**53**:1074–1077.
48. Legrain V, Taieb A, Sage T, Maleville J. Urticaria in infants: a study of forty patients. *Pediatr Dermatol* 1990;**7**:101–107.
49. Greaves MW. Chronic urticaria in childhood. *Allergy* 2000;**55**:309–320.
50. Bailey E, Shaker M. An update on childhood urticaria and angioedema. *Curr Opin Pediatr* 2008;**20**:425–430.
51. Novembre E, Cianferoni A, Mori F, Barni S, Calogero C, Bernardini R et al. Urticaria and urticaria related skin condition/disease in children. *Eur Ann Allergy Clin Immunol* 2008;**40**:5–13.

Appendix

Physicians and specialists who contributed on diagnosis and management of urticaria in the democratic process and discussion within the 3rd International Consensus Meeting on Urticaria, *Urticaria 2008*:

- | | |
|--|------------------------------------|
| Abd El Fattah, Ahmed (Dubai) | Ayala, Fabio (Italy) |
| Abdal Karim Mualem, Mohamad Gyas (Abu Dhabi) | Aydemir, Ertugrul (Turkey) |
| Abdallah, Mahmoud (Egypt) | Baiardini, Ilaria (Italy) |
| Abdollahnia, Mandana (Germany) | Balazs, Anna (Germany) |
| Aberer, Werner (Austria) | Baranov, Alexander (Russia) |
| Alborova, Alena (Germany) | Bendandi, Barbara (Italy) |
| Al Harthy, Aseela (Dubai) | Berberoglu, Harun (Turkey) |
| Altmayer, Anita (Hungary) | Bergmann, Karl-Christian (Germany) |
| Altrichter, Sabine (Germany) | Biedermann, Tilo (Germany) |
| Altunay, Ilknur Kivanc (Turkey) | Bielsa, Isabel (Spain) |
| Ardelean, Elena Angelica (Germany) | Blazek, Claudia (Germany) |
| Astner, Susanne (Germany) | Blaziene, Audra (Lithuania) |
| Atakan, Nilgun (Turkey) | Blume-Peytavi, Ulrike (Germany) |

Bona, Katalin (Hungary)
 Boodstein, Nikolai (Germany)
 Borzova, Elena (UK)
 Bräutigam, Matthias (Germany)
 Brockow, Knut (Germany)
 Brzoza, Zenon (Poland)
 Burbach, Guido (Germany)
 Chomiciene, Anzelika (Lithuania)
 Costa, Ana Célia (Portugal)
 Criton, Sebastian (India)
 Csonka, Péter (Finland)
 Danek, Krystyna (Poland)
 Danilycheva, Inna (Russia)
 Daschner, Alvaro George (Spain)
 De la Cuadra, Jesus (Spain)
 De Monchy, Jan (Netherlands)
 De Pità, Ornella (Italy)
 Degenhardt-Oehlert, Dagmar (Germany)
 Denes, Marta (Hungary)
 Douladiris, Nikolaos (Greece)
 Dronamraju Murthy, Butchi Narayana (India)
 Duarte, Fatima (Portugal)
 Dudeck, Anne (Germany)
 Ebermann, Nora (Germany)
 El Abd, Mohamad (Dubai)
 Fabos, Beata (Hungary)
 Ferran, Marta (Spain)
 Gabr, Mousa Salama (Kuwait)
 Galló, Melitta (Hungary)
 Ganjoo, Anil Kumar (India)
 Gavvala, Man Mohan (India)
 Gelmetti, Carlo (Italy)
 Gorge, N. D. (Dubai)
 Godse, Kiran Vasant (India)
 Grabbe, Jürgen (Germany)
 Grosber, Martine (Germany)
 Gul, Ulker (Turkey)
 Gupta, Rajinder Parshad (India)
 Gussmann, Felix (Germany)
 Güzelbey, Ozan (Germany)
 Habib, Douagui (Algeria)
 Hakim-Rad, Kayvan (Germany)
 Halvorsen, Ragnhild (Norway)
 Hamelmann, Eckard (Germany)
 Hampova, Darina (Czech Republic)
 Hanfland, Julia (Germany)
 Haraszti, Gabor (Hungary)
 Harold, Smeenge (Netherlands)
 Hartmann, Karin (Germany)
 Hawranek, Thomas (Austria)
 Heiberg, Jens (Denmark)
 Heine, Guido (Germany)
 Hoting, Edo (Germany)
 Humlová, Zuzana (Czech Republic)
 Hund, Martina (Germany)
 Hyry, Heli (Finland)
 Iamandescu, Ioan Bradu (Romania)
 Ilter, Nilsel (Turkey)
 Jaeger, Teresa (Germany)
 Jaffar, Huma (Bahrain)
 Jakob, Thilo (Germany)
 Janaki, Ramamurthy (India)
 Jung, Anja (Germany)
 Karolyi, Zsuzsanna (Hungary)
 Kasperska-Zajac, Alicja (Poland)
 Kay, A. Barry (UK)
 Kedikoglou, Simeon (Greece)
 Keßler, Birgit (Germany)
 Kibbi, Abdel Ghani (Lebanon)
 Klein, Georg (Austria)
 Kocatürk, Emek (Turkey)
 Kokhan, Muza (Russia)
 Kosnik, Mitja (Slovenija)
 Kostiainen, Minna (Finland)
 Koti, Ioanna (Germany)
 Kovago, Levente (Hungary)
 Krause, Karoline (Germany)
 Kukk, Terje (Estonia)
 Kuriyipe, Vallukandathil Peter (India)
 Lange, Michael (Germany)
 Larenas-Linnemann, Désirée (Mexico)
 Latuske, Ann-Marijke (Germany)
 Lawlor, Frances (UK)
 Lee, Hae-Hyuk (Germany)
 Lefebvre, Martine (Spain)
 Lehtmets, Ama (Estonia)
 Lilleeng, Mila (Norway)
 Lipowsky, Florian (Germany)
 Lora, Viviana (Italy)
 Lunder, Tomaz (Slovenija)
 Magerl, Markus (Germany)
 Malanin, Ken (Dubai)
 Malpani, Suneel (India)
 Manikas, Argiris (Greece)
 Manousakis, Emmanouil (Greece)
 Margari, Paraskevi (Greece)
 Marsland, Alexander (UK)
 Matthieu, Lucrèce (Belgium)
 Maurer, Gabriele (Germany)
 Mestdagh, Kristel (Belgium)
 Metz, Martin (Germany)
 Mitzel-Kaoukhov, Heidrun (Germany)
 Mlynek, Agnieszka (Poland)
 Mobacken, Hakan (Sweden)
 Môrete, Ana (Portugal)
 Mrabet-Dahbi, Salima (Germany)
 Mukesh, Girdhar (India)
 Mukesh, Raj (India)
 Munoz, Rosa M. (Spain)
 Namazova, Leila (Russia)
 Nast, Alexander (Germany)
 Oestmann, Elsbeth (Germany)
 Ollert, Markus (Germany)
 Olsen, Anne (Norway)

Zuberbier et al.

Onder, Meltem (Turkey)
Opper, Britta (Germany)
Ozturkcan, Serap (Turkey)
Pawliczak (Poland)
Pereira, Celso (Portugal)
Philipp, Sandra (Germany)
Pigatto, Paolo Daniele (Italy)
Popescu, Florin-Dan (Romania)
Raap, Ulrike (Germany)
Ramadan, Rana (Lebanon)
Rasche, Claudia (Germany)
Rzany, Berthold (Germany)
Romanska-Gocka (Poland)
Rosen, Karin (USA)
Rueff, Franziska (Germany)
Saarialho, Henna (Finland)
Sabato, Vito (Italy)
Sanjiv, Kandhari (India)
Santa, Marta Cristina (Portugal)
Schäfer, Torsten (Germany)
Schäfer-Hesterberg, Gregor (Germany)
Schmidt, Ute (Germany)
Schoepke, Nicole (Germany)
Scholz, Elisabeth (Germany)
Seefluth, Robina (Germany)
Seymons, Katy (Belgium)
Sharma, Rajeev (India)
Silvestre Salvador, Juan Francisco (Spain)
Sitkauskiene, Brigita (Lithuania)
Skov, Per Stahl (Denmark)
Sommerfeld, Beatrice (Sweden)

Soost, Stephanie (Germany)
Sorensen, Eva Valbjørn (Denmark)
Ständer, Harmut (Germany)
Ständer, Sonja (Germany)
Stefaniak, Richard (Germany)
Steinhoff, Matthias (Germany)
Stenmark, Särhammar Gunnel (Sweden)
Stockfleth, Eggert (Germany)
Szakos, Erzsébet (Hungary)
Szalai, Zsuzsanna (Hungary)
Szegedi, Andrea (Hungary)
Taskapan, Oktay (Turkey)
Teebi, Zaid (Malta)
Teichler, Angela (Germany)
Terzi, Seyma (Spain)
Trautinger, Franz (Austria)
Trefzer, Uwe (Germany)
Treiber, Nicolai (Germany)
Trosien, Julia (Germany)
Van der Valk, P.G.M. (Netherlands)
Varszegi, Dalma (Hungary)
Vestergaard, Christian (Denmark)
Vieira dos Santos, Rosaly (Germany)
Weller, Karsten (Germany)
Wieczorek, Dorothea (Germany)
Wöhrl, Stefan (Austria)
Wöllner, Kristina (Germany)
Worm, Margitta (Germany)
Wozniacka, Anna (Poland)
Zuberbier, Martina (Germany)