Allergy 2009: 64: 1427–1443

DOI: 10.1111/j.1398-9995.2009.02178.x

Position paper

EAACI/GA^{2}LEN/EDF/WAO guideline: management of urticaria

This guideline, together with its sister guideline on the classification of urticaria (Zuberbier T, Asero R, Bindslev-Jensen C, Canonica GW, Church MK, Giménez-Arnau AM et al. EAACI/GA^{2}LEN/EDF/WAO Guideline: definition, classification and diagnosis of urticaria. Allergy 2009;**64**: 1417–1426), is the result of a consensus reached during a panel discussion at the Third 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 (GA^{2}LEN), the European Dermatology Forum (EDF) and the World Allergy Organization (WAO). As members of the panel, the authors had prepared their suggestions regarding management of urticaria before the meeting. 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 reports of the first and the second symposia in 2000 and 2004. These suggestions were then discussed in detail among the panel members and with the over 200 international specialists of the meeting to achieve a consensus using a simple voting system where appropriate. Urticaria has a profound impact on the quality of life and effective treatment is, therefore, required. The recommended first line treatment is new generation, nonsedating H_1-antihistamines. If standard dosing is not effective, increasing the dosage up to four-fold is recommended. For patients who do not respond to a four-fold increase in dosage of nonsedating H_1-antihistamines, it is recommended that second-line therapies should be added to the antihistamine treatment. In the choice of second-line treatment, both their costs and risk/benefit profiles are most important to consider. Corticosteroids are not recommended for long-term treatment due to their unavoidable severe adverse effects. This guideline was acknowledged and accepted by the European Union of Medical Specialists (UEMS).

T. Zuberbier[1], R. Asero[2], C. Bindslev-Jensen[3], G. Walter Canonica[4], M. K. Church[1], A. M. Giménez-Arnau[5], C. E. H. Grattan[6], A. Kapp[7], M. Maurer[1], H. F. Merk[8], B. Rogala[9], S. Saini[10], M. Sánchez-Borges[11], P. Schmid-Grendelmeier[12], H. Schünemann[13], P. Staubach[14], G. A. Vena[15], B. Wedi[7]

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

Key words: consensus; guideline; treatment; urticaria; wheal.

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

Accepted for publication 3 July 2009

This guideline is the result of a panel discussion during the Third International Meeting on Urticaria, *Urticaria 2008*, a joint initiative of the EAACI Dermatology Section, GA^{2}LEN, EDF, and WAO.

Urticaria is a heterogeneous group of diseases that result from a large variety of underlying causes, are elicited by a great diversity of factors, and present clinically in a highly variable way. The aim of treatment,

however, is the same for all types of urticaria: to achieve complete symptom relief. The management of urticaria is best subdivided into two basic lines of approach both of which should be considered in each patient: first, the identification and elimination of the underlying cause(s) and/or eliciting trigger(s), and, second, treatment aimed at providing symptom relief.

Treating the cause is the most desirable option, but it is, unfortunately, not applicable in the majority of patients, especially in cases of inducible urticarias which are mainly idiopathic. Second best is avoidance of the eliciting trigger or stimulus, which can be instituted for the rare patients with IgE-mediated urticaria and partly, for those patients with physical urticaria. In the latter group, the impact of physical stimuli can be diminished and symptoms ameliorated by appropriate measures (e.g., cushioning in pressure urticaria). In spontaneous acute and chronic urticaria, treatment of associated infectious and/or inflammatory processes, including *Helicobacter pylori*-associated gastritis, parasitic diseases, or food and drug intolerance may be helpful in selected cases. In addition, it must be noted that some factors, e.g., analgesic drugs, can elicit new wheal formation as well as augment preexisting urticaria. Chronic urticaria is also recognized as stress – vulnerable disease in which psychological stress can trigger or increase itching. It is suggested that effective management process could take into account, at least in some of the patients, psychological factors (2–4). In all cases symptomatic relief should be offered while searching for causes.

Symptomatic treatment is currently the most frequently used form of management. It aims ameliorating or suppressing symptoms by inhibiting the release and/or the effect of mast cell mediators and possibly other inflammatory mediators.

The treatment options available have been evaluated in this guideline according to the following methods.

Methods

As members of the panel, the authors had prepared their suggestions regarding management of urticaria before the meeting. 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 reports of the first and second symposia in 2000 and 2004 (5, 6). These suggestions were then discussed in detail among the panel members and with the participants of the meeting, to achieve a consensus 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.

In the previous consensus document, studies were evaluated using the Methodology Checklist 2 for Randomized Controlled Trials (RCTs) of the Scottish Intercollegiate Guidelines Network (SIGN) resulting in the following 3-level code: ++, +, −. This code, together with the study type, decided the Level of Evidence (1++ to 1−, 2++ to 2−, 3, 4) that led to the Grade of Recommendation (A–D). However, the SIGN methodology does not assign a quality or level of evidence for the body of evidence and it is intended only for assessment of individual studies that are identified during the search process. However, in order to express the confidence in the totality of evidence an approach to assessing a body of evidence for a given questions is required. For the current guideline we used a pragmatic Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach transforming the already existing evaluations of the literature according to the SIGN criteria for individual studies from the previous guideline and adding newly published studies (Table 1). We based our ratings on the levels of evidence we obtained using the SIGN methodology from the previous guidelines without re-examining the assessments.

The key principle of the GRADE approach is to provide transparency and clear and explicit criteria for assessing the quality of evidence and grading the strength of recommendations (7–11). While recommendations in guidelines, in particular those developed

Table 1. Evidence of identified literature sources

The level of evidence provided by the study is derived from the code allocated for the methodological quality and the type of study, according to the Methodology Checklist 2: Randomized Controlled Trials of the Scottish Intercollegiate Guidelines Network (SIGN).

1^{++}	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2^{++}	High-quality systematic reviews of case–controlled or cohort or studies
	High quality case–controlled or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2^{+}	Well conducted case–controlled or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2^{-}	Case–controlled or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Nonanalytic studies, e.g., case reports, case series
4	Expert opinion

SIGN level of evidence	GRADE Quality of evidence
1^{++}	High
1^{+}	Moderate
1^{-}	Low
2^{++}	Low
2^{+}	Low
2^{-}	Very low
3	Very low
4	Very low

Abbreviations used in this and subsequent tables: AH, antihistamine; ns, nonsedating; RCT, randomized controlled trial; s, sedating, sg, second generation.
The following translation to the GRADE quality of evidence was used acknowledging that a more detailed assessment will possibly change the quality of evidence and that additional quality criteria are considered in GRADE.

with the GRADE approach, should ideally be based on well done systematic reviews, a more pragmatic approach to applying GRADE includes the identification of well done systematic reviews for a given clinical question or, alternatively, conducting a systematic review. An even more pragmatic approach includes the use of informal summaries based on searches of the literature. This should be followed by grading the quality of evidence and strength of each recommendation. The key principle is to be transparent about the methods, in particular those that are used for summarizing the evidence and the key factors influencing a recommendation.

For this Urticaria guideline 2008 update most of the sections did not follow systematic review methodology, but we did follow the general principles of GRADE for assessing the quality of evidence and strength of recommendations. Factors that influence the strength of a GRADE recommendation are the quality of the underlying evidence, the balance between desirable and undesirable effects and resources used for an intervention.

Separation of the strength of a recommendation from the quality of supporting evidence is critical when making recommendations. The GRADE system permits strong recommendations supported by low or very rarely very low quality evidence from downgraded RCTs or observational studies. At the same time allowing weak recommendations based on high-quality evidence. While the former is a rare occurrence in the unusual case where other factors than the evidence from included studies that determine the strength of a recommendation suggest this as the best course of action, weak recommendations in the face of high quality evidence are less unusual.

The guideline panel chose the words 'we recommend' – for strong recommendations and 'we suggest' – for weak recommendations in order to adhere to the same methodology as for development of the Allergic Rhinitis and its Impact on Asthma Guideline 2008 update (Table 2) (10). This same terminology has also been adhered to in those parts of the guideline where the assessment of the evidence was not done in full.

Literature searching for all questions was done using PubMed/MEDLINE and EMBASE together with hand-searching of abstracts of international allergy conferences in 2004–2008. We did not complete full systematic reviews for this guideline. Studies that had no English abstract were not systematically evaluated. Also excluded were those investigating terfenadine and astemizole, which have strong cardiotoxic effects.

Participants of the conference that led to formulation of recommendations were presented with a draft version of this document and were asked to vote whether they agreed with specific parts of the text that referred to therapeutic options. Voting was preceded by discussion if disagreement was present.

Table 2. Box of recommendations and suggestions for the management of urticaria

We recommend the use of the treatment algorithm as described in Fig. 1 for the symptomatic treatment of chronic spontaneous urticaria (strong, low quality evidence).

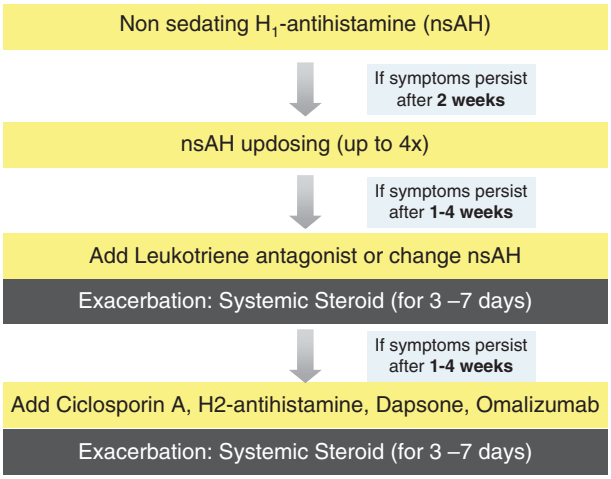
In patients with urticaria and no special indication, we recommend against the routine use of old sedating first generation antihistamines (strong recommendation, high quality evidence).

We recommend against the use of astemizole and terfenadine (strong recommendation, high-quality evidence).

We suggest the same first line treatment and up-dosing as described in Fig. 1 for children (weight adjusted) (weak recommendation, low-quality evidence).

We suggest the same first line treatment as described in Fig. 1 in pregnant or lactating women with chronic spontaneous urticaria but safety data in a large meta-analysis is limited to loratadine (weak recommendation, very low-quality evidence).

Remarks: higher doses may be required, but their safety profile needs to be carefully weighted against the potential additional benefit.



Comments on procedure on algorithm for chronic urticaria

First level: High quality evidence

- Low cost (worldwide availability also in developing countries mostly cheaper than old sedating Antihistamines)
- Very good safety profile
- Very good evidence for efficacy

Second level: Low quality evidence

- Low cost
- Good safety profile
- Good evidence for efficacy

Third level: Very low quality evidence

- Low –to medium-low cost
- Good safety profile
- Insufficient or no evidence for efficacy in high quality RCT

Fourth level:

- *Ciclosporin A:*
  - Medium to high cost
  - Moderate safety profile
  - Moderate level of evidence for efficacy
- *H2-Antihistamine:*
  - Low cost
  - Good safety profile
  - Very low level of evidence for efficacy
- *Dapsone:*
  - Low cost
  - Medium level of side effects
  - Low level of evidence for efficacy
- *Anti-IgE:*
  - High cost
  - Good safety profile
  - Low level evidence for good efficacy

Figure 1. Recommended treatment algorithm for chronic urticaria.

Strength of recommendation

Recommendations are classified as 'strong' or 'weak' recommendations, as recommended in the GRADE methodology. 'Strong' recommendations can be interpreted as:

- Most individuals should receive the intervention
- Most well informed individuals would want the recommended course of action and only a small proportion would not
- Could be used for policy making or as or quality indicator.

'Weak' recommendations can be interpreted as:

- The majority of well informed individuals would want the suggested course of action, but an appreciable proportion would not
- Widely varying values and preferences
- Policy making or quality indicator development will require extensive debates and involvement of many stakeholders.

Considerations about patient important outcomes in patients with urticaria

Quality of life

Health Related Quality of Life (HRQL) is increasingly recognized as a primary outcome in clinical trials, population studies and public health. Both physicians and researchers are aware that assessing HRQL impairment is a requirement for chronic conditions that do not lead to mortality changes or easily defined events. Generic HRQL instruments allow a complete assessment based on biomedical and socio-economic data in order to obtain a global evaluation of both disease and treatment. Specific HRQL instruments (e.g., disease or condition specific) allow the assessment of domains that are specific for a certain health problem (e.g., urticaria). The latter instruments are generally more responsive to change in HRQL but they generally do not cover all relevant domains for a comprehensive assessment of HRQL.

While HRQL has been extensively assessed in numerous dermatological and allergic conditions, a literature search shows that only few studies evaluate this topic in patients with chronic spontaneous urticaria and virtually no studies on HRQL are available for other types and subtypes of urticaria (12). The available data indicate that urticaria has a detrimental effect on both objective functioning and subjective well-being. For example, O'Donnell et al. showed that health status scores in patients with chronic spontaneous urticaria are comparable to those reported from patients with coronary artery disease (13). Furthermore, both health status and subjective satisfaction in patients with chronic spontaneous urticaria is lower than in healthy subjects and in patients with respiratory allergy (14). A study of Poon et al. focused on the extent and nature of disability in different types of urticaria, showing a large variation in HRQL scores within different urticarial subsets (12).

In these mentioned studies, the assessment of HRQL was performed by using generic questionnaires (applicable to all health conditions) and by specialty specific questionnaire (developed for skin diseases). There was only one disease specific questionnaire applied in patients with chronic urticaria, but it has not been validated (13).

Recently a questionnaire specifically developed for chronic spontaneous urticaria has been validated, including physical, emotional, social, and practical aspects that characterize this condition (15). The aim was to offer the research community a sensible and simple tool to evaluate specifically HRQoL in urticaria patients. This new tool named Chronic Urticaria Quality of Life Questionnaire (CU-Q_2oL) was generated and tested in the Italian language following well established procedures and applied to other similar instruments. The CU-Q_2oL met the standards for validity with good construct validity, internal consistency, reliability, and responsiveness. These psychometric characteristics make the new questionnaire suitable for the assessment of the health burden of both chronic spontaneous urticaria and its treatment. It has now been translated and validated in German and Spanish. Polish, Turkish, Greek, Bulgarian, and English versions are currently being validated (16, 17).

Management of urticaria

Identification and elimination of the underlying cause and/or trigger

With the use of this therapeutic approach, an exact diagnosis is a basic prerequisite, see the sister guideline on the definition, classification, and diagnosis of urticaria (1), which is just like this guideline based on the previously published consensus (18).

If remission, following elimination of the suspected agent occurs, only recurrence of symptoms in a double-blind provocation test will provide definitive proof of its causative nature since spontaneous remission of urticaria might also occur incidentally in parallel with, but not because of, the elimination of a suspected cause or trigger.

Identifying the cause of urticaria is not, however, easily possible in most cases, e.g. infections may be a cause, aggravating factor or unassociated bystander.

Drugs. When such agents are suspected in the course of diagnosis, they should be omitted entirely or substituted by another class of agents if indispensable. Drugs causing nonallergic hypersensitivity reactions (the prototypes being nonsteroidal anti-inflammatory drugs and angiotensin converting enzyme-inhibitors-inhibitors) cannot only elicit, but can also aggravate preexisting chronic spontaneous urticaria (19), so that elimination will only improve symptoms.

Physical stimuli. Avoidance of physical stimuli for the treatment of physical urticaria is desirable, but not always simple. Detailed information about the physical properties of the respective stimulus should make the patient sufficiently knowledgeable to recognize and control exposure in normal daily life. Thus, it is important in delayed pressure urticaria and in symptomatic dermographism/urticaria factitia to point out that pressure is defined as force per area and that simple devices, such as broadening of the handle of heavy bags for pressure urticaria or reducing friction in case of symptomatic dermographism/urticaria factitia, may already be helpful in the prevention of symptoms. Similar considerations hold for cold urticaria where the impact of the chill factor in cold winds needs to be remembered. For solar urticaria, the exact identification of the range of eliciting wave

lengths may be important for the appropriate selection of sunscreens or for the selection of light bulbs with a UV-A filter. However, in many patients, the threshold for the relevant physical trigger is low and total avoidance of symptoms is virtually impossible. Severe dermographic urticaria is sometimes confused with chronic urticaria because seemingly spontaneous hives are observed where even loose-fitting clothing rubs on the patient's skin.

Eradication of infectious agents and treatment of inflammatory processes. In contrast to physical urticaria where co-existing, potentially disease-sustaining factors are only found occasionally in cold and dermographic urticaria (symptomatic dermographism/urticaria factitia), chronic spontaneous urticaria is often reported to be associated with a variety of inflammatory or infectious diseases. This is regarded as significant in some instances. These infections, which should be treated appropriately, include those of the gastrointestinal tract like *H. pylori* (20, 21) or bacterial infections of the nasopharynx. Bowel parasites, a rare possible cause of chronic spontaneous urticaria in developed industrial countries, should be eliminated (22). In the past, intestinal candidiasis was regarded as a highly important underlying cause of chronic spontaneous urticaria (23), but more recent findings fail to support a significant causative role (24). Apart from infectious diseases, chronic inflammatory processes due to diverse other diseases have been identified as potentially causative for chronic spontaneous urticaria in the recent past. This holds particularly for gastritis, reflux oesophagitis or inflammation of the bile duct or gall bladder (24, 25). However similar to infections, it is not easily possible to discern whether any of these are etiologic or a chance association.

Reduction of functional autoantibodies. There is still only little experience in the treatment of chronic spontaneous urticaria by direct reduction of functional autoantibodies by plasmapheresis, which has been shown to be of temporary benefit in individual, severely affected patients (26, 27). Due to high costs, this therapy is suggested for autoantibody-positive chronic spontaneous urticaria patients who are unresponsive to all other forms of treatment. However, there is good and increasing evidence about the effectiveness of immunomodulating therapies, such as ciclosporin (28–31), that inhibit antibody formation as one of their actions. Other immunomodulatory therapies, for which less evidence is available, include intravenous immunoglobulins (IVIG), methotrexate, azathioprine, mycophenolate, mofetil, cyclophosphamide, anti-IgE (Omalizumab), and tacrolimus (see Table 3).

Dietary management. IgE-mediated food allergy is rarely the underlying cause of chronic spontaneous urticaria (24, 32). If identified, the specific food allergens need to be omitted as far as possible. In a subgroup of chronic spontaneous urticaria patients, pseudoallergic reactions (non-IgE-mediated hypersensitivity) to naturally occurring food ingredients and in some cases to food additives are seen (24, 32–34). Similar to drugs, pseudoallergens can both elicit and aggravate chronic spontaneous urticaria (35). In these cases a diet containing only low levels of natural as well as artificial food pseudoallergens should be instituted and maintained for a prolonged period, at least 3–6 months. During this time, remission is achieved in approximately 50% of patients. It should be underlined that avoidance of type I-allergens clears urticaria symptoms within 24–48 h if the relevant allergens are eliminated rapidly, whereas in pseudoallergy, a diet must often be maintained for a minimum of 3 weeks before beneficial effects are observed. Detailed information about dietary control can be found in the referenced manuscripts. However, it should be pointed out that success rate may vary considerably due to regional differences in food and dietary habits. More research is necessary on the effect of foodstuffs in causing urticaria, particularly in areas where the daily diet is greatly different to that to that in Western Europe.

Symptomatic therapy

Induction of tolerance may be considered in some types of urticaria where a mast cell-mediated mechanism is at least partly implicated. Examples are cold urticaria, cholinergic urticaria, and solar urticaria, where even a rush therapy with UV-A has been proven to be effective within 3 days (36).

The main option, however, in therapies aimed at symptomatic relief is to reduce the effect of mast cell mediators on the target organs. Many symptoms of urticaria are mediated primarily by the actions of histamine on H_1-receptors located on endothelial cells (the wheal) and on sensory nerves (neurogenic flare and pruritus). Thus, H_1-antihistamines are of eminent importance in the treatment of urticaria. However in some cases, especially of chronic urticaria, a pronounced cellular infiltrate may be observed. These may respond completely to a brief burst of corticosteroid and may be relatively refractory to antihistamines.

Antihistamines have been available for the treatment of urticaria since the 1950s. However, the older first generation antihistamines have pronounced anticholinergic effects and sedative actions on the central nervous system (CNS) which last longer than 12 h whereas the antipruritic effects last only for 4–6 h. Consequently, many interactions have been described for these sedating antihistamines with alcohol and drugs affecting the CNS, such as analgesics, hypnotics, sedatives, and mood elevating drugs. Also, monoamine oxidase inhibitors can prolong and intensify the anticholinergic effects of these drugs. In addition, first generation antihistamines can interfere with rapid eye movement (REM) sleep and impact on learning and performance. We recommend against the use of these sedating antihistamines for the routine management of chronic urticaria as first line agents, except for the rare places worldwide in which nonsedating antihistamines

Table 3. Treatments in urticaria

Patient population	Intervention	Quality of evidence[b]	Strength of recommendation for use of intervention	Reference	Alternative interventions (for patients who do not respond to other interventions)	Quality of evidence[b]	Strength of recommendation for use of intervention	Reference
a. Acute spontaneous urticaria	ns sg H1-AH: I	Low	Strong	(48, 71)	Prednisolone, 2 × 20 mg/day* for 4 days	Low	Weak	(72)
					Prednisolone, 50 mg/day* for 3 days	Very low		(48)
					H_2-blocker, single dose for 5 days	Very low		(73–75)
b. Chronic spontaneous urticaria	ns sg H1-AH - Increase dosage if necessary up to four-fold	High Low	Strong Weak	(76–112) (111, 112) (47, 113)	ns sg H_1-AH and ciclosporin	High	All weak	(28, 50, 114)
					ns sg H_1 and H_2-AH			
					Cimetidine	Very low		(115–118)
					Monotherapy			
					Tricyclic antidepressants (doxepin)	Low		(119–121)
					Ketotifen	Low		(122)
					Hydroxychloroquine	Very low		(123)
					Dapsone	Very low		(124, 125)
					Sulfasalazine	Very low		(126)
					Methotrexate	Very low		(126)
					Corticosteroids	Very low		(127, 128)
					Other treatment options			
					Combination therapy			(129)
					ns sg H_1-AH and stanazolol	Low		(130)
					ns sg H_1-AH and zafirlukast	Very low		
					ns sg H_1-AH and Mycophenolate mofetil	Very low		(131) (51)
					ns sg H_1-AH and narrowband UV-B	Very low		(55, 59, 132–134)
					ns sg H_1-AH and omalizumab	Very low		
					Monotherapy			
					Oxatomide	Very low		(135–137)
					Nifedipine	Very low		(138)
					Warfarin	Very low		(139, 140)
					Interferon	Very low		(141, 142)
					Plasmapheresis	Very low		(26, 143)
					Immunoglobulins	Very low (63)		
					Autologs whole blood Injection (ASST positive only)	Very low (144, 145)		
c. Physical urticaria	Avoidance of stimuli	High	Strong	No controlled studies but very strong effects in observational studies				
Symptomatic dermographism/ Urticaria factitia	ns sg H_1-AH:	Low	Weak	(146, 147)	Ketotifen (see also chronic urticaria)	Very low	All weak	(148)
					Narrowband UV-B therapy	Very low		(54)
Delayed pressure urticaria	ns sg H_1-AH: Cetirizine High dose ns H_1-AH	Low Very low Very low	All weak	(40, 149)	Combination therapy			
					Montelukast and ns H_1-AH (loratadine)	Very low	All weak	(150)
					Monotherapy			
					Prednisolone 40–20 mg*	Very low		(151)
					Other treatment options			
					Combination therapy			
					Ketotifen and nimesulide	Very low		(151)
					Monotherapy			
					Topical clobetasol propionate	Very low		(152, 153)
					Sulfasalazine	Very low		(154)

Table 3. (Continued)

Patient population	Intervention	Quality of evidence[b]	Strength of recommendation for use of intervention	Reference	Alternative interventions (for patients who do not respond to other interventions)	Quality of evidence[b]	Strength of recommendation for use of intervention	Reference
Cold urticaria	ns sg H_1-AH	High	Strong	(113, 155–159)	Trial with penicillin i.m./p.o.	Very low	All weak	(160)
	Increase dose up to four-fold			(113)	Trial with doxycyline p.o.	Very low		(160)
					Induction of physical tolerance.			(160)
					Other treatment options	Very low		(41, 161)
					Cyproheptadine	Low		(162)
					Ketotifen	Very low		(163, 164)
					Montelukast			
Solar urticaria	ns H_1-AH	Very low	Weak	(165, 166)	Induction of physical tolerance	Very low	All weak	(36)
					Other treatment options			
					Plasmapheresis + PUVA	Very low		(167)
					Photopheresis	Very low		(168)
					Plasma exchange	Very low		(169)
					IVIGs	Very low		(170, 171)
					Omalizumab	Very low		(58)
d. Special types of inducible urticaria								
Cholinergic urticaria	ns H_1-AH	Low	Weak	(172)	'Exercise tolerance'	Very low	All weak	
	– Increase dosage if necessary	Low		(173)	*Other treatment options*			
					Ketotifen	Very low		(148)
					Danazol	Very low		(174)
					Omalizumab	Very low		(56)

[b]The quality of evidence was translated from the SIGN method to GRADE without re-review of the individual studies. See Table 1.
*Recommendation refers to treatment of adult patients.

are not available or in special situations where they prove to be more effective or better tolerated than nonsedating H_1-antihistamines. This recommendation is based on strong evidence regarding potentially serious side-effects of old sedating antihistamines and the availability of new generation nonsedating antihistamines which not only lack these side-effects but also have a higher efficacy and duration of action. The worst side-effects are observed with promethazine, diphenhydramine and chlorpheniramine. Hydroxyzine (which is the sedating parent drug of the metabolite cetirizine) at 25–50 mg four times daily (equal to 4–8 cetirizine tablets daily) may be tried by specialists prior to consideration of more toxic agents but patients need to be informed of side-effects (37, 38).

The development of second generation antihistamines led to drugs which are minimally sedating and free of anticholinergic effects. However, two of the earlier second generation drugs, astemizole and terfenadine, which were essentially pro-drugs requiring hepatic metabolism to become fully active, had cardiotoxic effects if this metabolism was blocked by concomitant administration of ketoconazole or erythromycin. These two drugs are no longer available in most countries and we recommend that they are not used.

Further progress with regard to drug safety was achieved by the development of the new generation antihistamines cetirizine, desloratadine, and fexofenadine, which are essentially nonsedating metabolites of earlier sedative antihistamines. More recently, levocetirizine, the active enantiomer of cetirizine, acrivastine, ebastine, and mizolastine have been added to the list of second generation antihistamines. Thus, considering their good safety profile, second generation antihistamines should be considered as the first line symptomatic treatment for urticaria. However, up to date, well designed clinical trials comparing efficacy and safety of individual nonsedating H_1-antihistamines in chronic spontaneous urticaria are largely lacking.

There are some studies showing the benefit of a higher dosage of antihistamines in individual patients (39, 40) corroborating earlier studies which came to the same conclusion employing first generation antihistamines (41, 42). This has been verified in studies using even up to four-fold higher than recommended doses of levocetirizine, desloratadine, and rupatadine (40, 43–45). Interestingly, however, Asero (46) reported that increasing the dose for chronic spontaneous urticaria of cetirizine three-fold did not produce further efficacy in severely affected patients. Furthermore, a recent study showed an incremental benefit of using levocetirizine at doses up to four-fold higher than the recommended dose in the majority of patients while in 10–15% antihistamines, even at these higher doses, did not produce any observable clinical effects (47).

In summary, these studies suggest that the majority patients with urticaria will profit from up-dosing with antihistamines although further research is needed for predicting factors in different subtypes of urticaria.

Further therapeutic possibilities

While antihistamines provide symptomatic treatment primarily by reducing the effect of histamine blood vessels and nerves, newer data suggest modern second generation nonsedating antihistamines may have anti-inflammatory effects. Whether this results from inhibition of the pro-inflammatory effects of histamine or from other effects of antihistamines is not yet clear.

At present, corticosteroids are frequently used in allergic diseases. There is a strong recommendation against the long-term use of corticosteroids outside specialist clinics if it can be avoided. If not, referral to specialists at urticaria centers is advised For acute urticaria and acute exacerbations of chronic spontaneous urticaria, a short course of corticosteroids may, however, be helpful to reduce disease duration (48). Nevertheless, well-designed RCTs are lacking.

Ciclosporin also has a moderate, direct effect on mast cell mediator release (49) and is the only agent of this type to inhibit basophil histamine release. Efficacy of ciclosporin in combination with a nonsedating H_1-antihistamine has been shown in two placebo controlled trials (28, 50) as well as in open controlled trials, but this drug cannot be recommended as standard treatment due to a high incidence of adverse effects. It is recommended only for patients with severe disease refractory to any dose of antihistamine. Ciclosporin has a far better risk/benefit ratio compared with steroids.

Phototherapy reduces the numbers of mast cells in the upper dermis. It has been successfully used in mastocytosis and is helpful in treatment-resistant patients with this condition (51, 52). For the treatment of chronic spontaneous urticaria and symptomatic dermographism, UV-A and UV-B treatment for 1–3 months can be added to antihistamine treatment (53, 54).

Omalizumab (anti-IgE) has now been shown to be dramatically effective in selected patients with chronic spontaneous urticaria (55), cholinergic urticaria (56), cold urticaria (57), and solar urticaria (58, 59). Larger double-blind placebo-controlled studies are needed to confirm these results. Antagonists of tumor necrosis factor α (TNFα) (60) and IVIG (61–63), which have been successfully used in case reports, are recommended currently only to be used in specialized centers as last option (i.e., anti-TNFα for delayed pressure urticaria and IVIG for chronic spontaneous urticaria).

While antihistamines at up to quadruple the manufacturers' recommended dosages will control symptoms in the majority of patients with urticaria in general practice, alternative treatments are needed for the remaining unresponsive patients. Before changing to an alternative therapy, it is recommended to wait for 1–4 weeks to allow full effectiveness of the antihistamines before considering referral to a specialist.

Since the severity of urticaria may fluctuate, and since spontaneous remission may occur at any time, it is also recommended to re-evaluate the necessity for continued or alternative drug treatment every 3–6 months.

Except for ciclosporin, which has restrictions due to its high cost and poor side-effect profile, many of the alternative methods of treatment, such as combinations of nonsedating H_1-antihistamines with H_2-antihistamines or with antileukotrienes, are based on RCTs with low levels of evidence (Table 3). The same holds true for monotherapy with ketotifen, montelukast, warfarin, and hydroxychloroquine. In addition, evidence from older data investigating oxatomide, doxepin, and nifedipine is poor.

For dapsone, sulfasalazine, methotrexate, interferon, plasmapheresis and IVIG only uncontrolled trials or case series have been published (Table 3).

Recent RCTs have addressed the use of antileukotrienes (Tables 3 and 4). Studies are difficult to compare due to different populations studied, e.g., inclusion of only aspirin and food additive intolerant patients or exclusion of autologs serum skin test positive patients.

On the other hand, some treatment alternatives formerly proposed have been shown to be ineffective in double-blind, placebo controlled studies and should no longer be used (although grade of recommendation is low). These include tranexamic acid and sodium cromoglicate (SCG) in chronic spontaneous urticaria (64, 65), nifedipine in symptomatic dermographism/urticaria factitia (66) and colchicine and indomethacin in delayed pressure urticaria (67, 68).

Table 3 summarizes the level of evidence of the current standard drug treatment and alternatives in several subtypes of urticaria, whereas Table 4 summarizes ineffective drugs or a combination of drugs in controlled trials.

Taken together, recommendations based on very high level of evidence exist only for symptomatic therapy with nonsedating antihistamines. However, it should be considered that these drugs are insufficient in some patients with urticaria and that RCTs often included patients with mild to moderate disease only. In contrast, most alternatives have been tested in patients previously not responding to antihistamines.

Thus, we clearly need more and well-designed RCTs to recommend or refuse potential alternatives.

Treatment of special populations

Children

Many clinicians use first generation, sedating H_1-antihistamines as their first choice in the treatment of children

Table 4. Quality of evidence and strength of recommendation not to use this intervention should not be administered because the downsides outweigh the potential benefits clearly

Type of urticaria	Intervention	Quality of evidence[b]	Strength of recommendation against that therapy	Reference
b. Chronic spontaneous urticaria	H_1-combination of sedating AH and H_2-AH cimetidine	Very low	All strong	(116)
	Sedating H_1-AH and ß-sympathomimetic terbutaline	Very low		(117, 175)
	Leukotriene antagonist montelukast alone	Low		(176)
	Addition of montelukast to nonsedating H_1-AH (desloratadine)	Low		(176)
	Leukotriene antagonist zafirlukast	Low		(177)
	Tranexamic acid	Very low		(65)
	Sodium cromoglicate	Very low		(64)
c. Physical urticaria				
Delayed pressure urticaria	Colchicine	Very low	All strong	(67)
	Indomethacin	Very low		(68)
Symptomatic dermographism/ Urticaria factitia	Addition of H_2-AH to SedatingH_1-AH or nonsedating H_1-AH	Very low	All strong	(178, 179)
	Nifedipine	Very low		(66)

[b]The quality of evidence was translated from the SIGN method to GRADE without re-review of the individual studies. See Table 1.

with allergies assuming that the safety profile of these drugs is better known than that of the second generation, nonsedating H_1-antihistamines due to a longer life on the market. Also, the use of nonsedating H_1-antihistamines is not licensed for use in children less than 6 months of age while the recommendation for the first generation H_1-antihistamines is sometimes less clear since these drugs were licensed at a time when the code of good clinical practice for the pharmaceutical industry was less stringent. As a consequence many doctors choose first generation antihistamines which, as pointed out above, have a lower safety profile compared with nonsedating H_1-antihistamines. A strong recommendation was made by the panel to discourage the use of first generation antihistamines in infants and children. Thus, in children the same first line treatment and up-dosing (weight adjusted) is recommended as in adults.

Pregnant women

The same considerations in principle apply to pregnant and lactating women. On one hand, use of any systemic treatment should generally be avoided in pregnant women, especially in the first trimester. On the other hand, pregnant women have the right to best possible therapy. While the safety of treatment has not been systematically studied in pregnant women with urticaria, it should be pointed out that the possible negative effects of increased levels of histamine occurring in urticaria have also not been studied in pregnancy. Regarding treatment, no reports of birth defects in women having used second generation antihistamines during pregnancy have been reported up to date. However, only small sample size studies are available for cetirizine (69) and one meta-analysis for loratadine (70). Furthermore, as several second generation antihistamines are now prescription free and used widely in both in allergic rhinitis and urticaria, it must be assumed that many women have used these drugs especially in the beginning of pregnancy, at least before the pregnancy was confirmed. Nevertheless, since the highest safety is mandatory in pregnancy, the suggestion for the use of second generation antihistamines should be limited to loratadine with the possible extrapolation to desloratadine. The increased dosage of second generation antihistamines can only be carefully suggested in pregnancy since safety studies have not been done and with loratadine it must be remembered that this drug is metabolized in the liver. First generation agents may be cautiously employed when symptoms dictate in the face of nonresponse to second generation antihistamines.

Limitations of these guidelines

The main limitation is the lack of a more detailed assessment of the quality criteria for individual studies. Furthermore, the translation of SIGN to GRADE should have been done with greater care and re-evaluation of the studies. However, we placed greater importance on avoiding confusion that would have resulted from using different systems to assess the quality of evidence and on harmonizing grading in general, then on the re-evaluation of all studies. Future updates of this guideline will include more detailed assessments of the evidence, possibly evidence summaries or profiles and a more structured approach to formulating and deciding about recommendations.

Conclusions

Quality of life in urticaria patients is severely affected and management of the disease should, therefore, be prompt and involve close cooperation between patient and physician. The aim of treatment is to achieve the absence of and complete protection from symptoms. Due to the high variability of disease severity, an individual approach is necessary for each patient. As a first line, triggering factors should be identified and avoided as far as possible and any associated diseases should be treated. The following treatment options exist and are discussed in detail in the text: second generation antihistamines (including up to four-fold higher; corticosteroids in severely affected patients; ciclosporin for patients refractory to other modalities). First generation sedating antihistamines should no longer be used as initial therapy except in those few countries where second generation antihistamines are not available or where their use outweigh their risks. Since the severity of urticaria may fluctuate and spontaneous remission may occur at any time, it is also important that the necessity for continued or alternative drug treatment is re-evaluated every 3–6 months.

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 Voigtmann, Germany), and the WAO and European Federation of Allergy and Airways Diseases Patients Association (EFA). The Global Allergy and Asthma European Network (GA^2LEN), contract n° 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 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. The authors would like to thank Martin Metz and Markus Magerl, Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Germany, for their efficient organisation 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

1. Zuberbier T, Asero R, Bindslev-Jensen C, Canonica GW, Church MK, Giménez-Arnau AM et al. EAACI/GA^2LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. Allergy 2009;**64**:1417–1426.
2. Brzoza Z, Kasperska-Zajac A, Badura-Brzoza K, Matysiakiewicz J, Hese RT, Rogala B. Decline in dehydroepiandrosterone sulfate observed in chronic urticaria is associated with psychological distress. Psychosom Med 2008;**70**: 723–728.
3. Owoeye OA, Aina OF, Omoluabi PF, Olumide YM. An assessment of emotional pain among subjects with chronic dermatological problems in Lagos, Nigeria. Int J Psychiatry Med 2007;**37**:129–138.
4. Arck P, Paus R. From the brain-skin connection: the neuroendocrine-immune misalliance of stress and itch. Neuroimmunomodulation 2006;**13**: 347–356.
5. Zuberbier T, Greaves MW, Juhlin L, Merk H, Stingl G, Henz BM. Management of urticaria: a consensus report. J Investig Dermatol Symp Proc 2001;**6**:128–131.
6. Zuberbier T, Bindslev-Jensen C, Canonica W, Grattan CE, Greaves MW, Henz BM et al. EAACI/GA2LEN/EDF guideline: management of urticaria. Allergy 2006;**61**:321–331.
7. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A et al. Going from evidence to recommendations. BMJ 2008;**336**: 1049–1051.
8. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is ''quality of evidence'' and why is it important to clinicians? BMJ 2008;**336**:995–998.
9. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;**336**: 924–926.
10. Brozek JL, Baena-Cagnani CE, Bonini S, Canonica GW, Rasi G, van Wijk RG et al. Methodology for development of the allergic rhinitis and its impact on asthma guideline 2008 update. Allergy 2008;**63**:38–46.
11. Schunemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A et al. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. Am J Respir Crit Care Med 2006;**174**: 605–614.
12. Poon E, Seed PT, Greaves MW, Kobza-Black A. The extent and nature of disability in different urticarial conditions. Br J Dermatol 1999;**140**: 667–671.
13. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. Br J Dermatol 1997;**136**:197–201.

14. 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.
15. Baiardini I, Pasquali M, Braido F, Fumagalli F, Guerra L, Compalati E et al. A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-QoL). Allergy 2005;**60**: 1073–1078.
16. Mlynek A, Magerl M, Hanna M, Lhachimi S, Baiardini I, Canonica GW et al. The German version of the chronic urticaria quality-of-life questionnaire: factor analysis, validation, and initial clinical findings. Allergy 2009;**64**:927–936.
17. Valero A, Herdman M, Bartra J, Ferrer M, Jauregui I, Davila I et al. Adaptation and validation of the Spanish version of the chronic urticaria quality of life questionnaire (CU-Q2oL). J Investig Allergol Clin Immunol 2008;**18**:426–432.
18. Zuberbier T, Bindslev-Jensen C, Canonica GW, Grattan CE, Greaves MV, Henz BM et al. EAACI/GA^{2}LEN/EDF guideline: definition, classification and diagnosis of urticaria. Allergy 2006; **61**:316–320.
19. Mathelier-Fusade P. Drug-induced urticarias. Clin Rev Allergy Immunol 2006;**30**:19–23.
20. Wedi B, Kapp A. *Helicobacter pylori* infection in skin diseases: a critical appraisal. Am J Clin Dermatol 2002;**3**:273–282.
21. Wedi B, Raap U, Kapp A. Chronic urticaria and infections. Curr Opin Allergy Clin Immunol 2004;**4**: 387–396.
22. Henz BM, Zuberbier T, Grabbe J, Monroe E, editors. Urticaria. clinical, diagnostic and therapeutic aspects. Causes of urticaria: Springer, 1998; 19–38.
23. Champion RH, Roberts SO, Carpenter RG, Roger JH. Urticaria and angio-oedema. A review of 554 patients. Br J Dermatol 1969;**81**:588–597.
24. Zuberbier T, Chantraine-Hess S, Hartmann K, Czarnetzki BM. Pseudoallergen-free diet in the treatment of chronic urticaria. A prospective study. Acta Derm Venereol 1995;**75**:484–487.
25. Vena GA, Puddu P, editors. Proceedings of the international symposium on urticaria. Bari: Publ. Scientif., 1998: 85–89.
26. Grattan CE, Francis DM, Slater NG, Barlow RJ, Greaves MW. Plasmapheresis for severe, unremitting, chronic urticaria. Lancet 1992;**339**:1078–1080.
27. Greaves M. Chronic urticaria. J Allergy Clin Immunol 2000;**105**:664–672.
28. Grattan CE, O'Donnell BF, Francis DM, Niimi N, Barlow RJ, Seed PT et al. Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. Br J Dermatol 2000;**143**:365–372.
29. Barlow RJ, Black AK, Greaves M. Treatment of severe, chronic urticaria with cyclosporine A. Eur J Dermatol 1993;**3**:273–275.
30. Fradin MS, Ellis CN, Goldfarb MT, Voorhees JJ. Oral cyclosporine for severe chronic idiopathic urticaria and angioedema. J Am Acad Dermatol 1991;**25**:1065–1067.
31. Toubi E, Blant A, Kessel A, Golan TD. Low-dose cyclosporin A in the treatment of severe chronic idiopathic urticaria. Allergy 1997;**52**:312–316.
32. Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. Br J Dermatol 1981;**104**:369–381.
33. Pfrommer C, Bastl R, Vieths S, Ehlers I, Henz BM, Zuberbier T. Characterization of naturally occurring pseudoallergens causing chronic urticaria. J Allergy Clin Immunol 1996;**97**:367.
34. Pigatto PD, Valsecchi RH. Chronic urticaria: a mystery. Allergy 2000;**55**:306–308.
35. Nettis E, Colanardi MC, Ferrannini A, Tursi A. Sodium benzoate-induced repeated episodes of acute urticaria/angio-oedema: randomized controlled trial. Br J Dermatol 2004;**151**:898–902.
36. Beissert S, Stander H, Schwarz T. UVA rush hardening for the treatment of solar urticaria. J Am Acad Dermatol 2000;**42**:1030–1032.
37. Kaplan A. Urticaria and angioedema. pathogenic mechanisms and treatment. JACI 2004;**114**:415–424.
38. Kaplan AP. Clinical practice. Chronic urticaria and angioedema. N Engl J Med 2002;**346**:175–179.
39. Zuberbier T, Munzberger C, Haustein U, Trippas E, Burtin B, Mariz SD et al. Double-blind crossover study of high-dose cetirizine in cholinergic urticaria. Dermatology 1996;**193**:324–327.
40. Kontou-Fili K, Maniakatou G, Demaka P, Paleologos G. Therapeutic effect of cetirizine 2HCl in delayed pressure urticaria. Health Sci Rev 1989;**3**:23–25.
41. Wanderer AA, Ellis EF. Treatment of cold urticaria with cyproheptadine. J Allergy Clin Immunol 1971;**48**:366–371.
42. Kaplan AP, Gray L, Shaff RE, Horakova Z, Beaven MA. In vivo studies of mediator release in cold urticaria and cholinergic urticaria. J Allergy Clin Immunol 1975;**55**:394–402.
43. Staevska M, Popov T, Kralimarkova T, Lazarova C, Kraeva S, Popova D et al. The effectiveness of antihistamines in up to four-times conventional doses in difficult-to-treat urticaria. Br J Clin Pharmacol 2009; (in press).
44. Siebenhaar F, Degener F, Zuberbier T, Martus P, Maurer M. High-dose desloratadine decreases wheat volume and improves cold provocation thresholds as compared with standard dose treatment in patients with acquired cold urticaria: a randomized, placebo-controlled, crossover study. J Allergy Clin Immunol 2009;**123**:672–679.
45. Gimenez-Arnau A, Izquierdo I, Maurer M. The use of a responder analysis to identify clinically meaningful differences in chronic urticaria patients following placebo-controlled treatment with rupatadine 10 and 20 mg. J Eur Acad Dermatol Venereol 2009;**23**:1088–1091.
46. Asero R. Chronic unremitting urticaria: is the use of antihistamines above the licensed dose effective? A preliminary study of cetirizine at licensed and above-licensed doses Clin Exp Dermatol 2007;**32**:34–38.
47. Church DS, Baiardini I, Staevska M, Popov T, Kralimarkova T, Dimitrov V et al. The effectiveness of antihistamines in up to four-times conventional doses on urticarial discomfort and quality of life in difficult-to-treat urticaria. Abstract 1501, Warsaw: XXVIII EAACI Congress, 2009.
48. Zuberbier T, Ifflander J, Semmler C, Henz BM. Acute urticaria: clinical aspects and therapeutic responsiveness. Acta Derm Venereol 1996;**76**:295–297.
49. Stellato C, de Paulis A, Ciccarelli A, Cirillo R, Patella V, Casolaro V et al. Anti-inflammatory effect of cyclosporin A on human skin mast cells. J Invest Dermatol 1992;**98**:800–804.
50. Vena GA, Cassano N, Colombo D, Peruzzi E, Pigatto P. Cyclosporine in chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. J Am Acad Dermatol 2006;**55**: 705–709.
51. Engin B, Ozdemir M, Balevi A, Mevlitoglu I. Treatment of chronic urticaria with narrowband ultraviolet B phototherapy: a randomized controlled trial. Acta Derm Venereol 2008;**88**:247–251.

52. Horio T. Indications and action mechanisms of phototherapy. J Dermatol Sci 2000;**23**:S17–S21.
53. Hannuksela M, Kokkonen EL. Ultraviolet light therapy in chronic urticaria. Acta Derm Venereol 1985;**65**:449–450.
54. Borzova E, Rutherford A, Konstantinou GN, Leslie KS, Grattan CE. Narrowband ultraviolet B phototherapy is beneficial in antihistamine-resistant symptomatic dermographism: a pilot study. J Am Acad Dermatol 2008;**59**:752–757.
55. Spector SL, Tan RA. Effect of omalizumab on patients with chronic urticaria. Ann Allergy Asthma Immunol 2007;**99**:190–193.
56. Metz M, Bergmann P, Zuberbier T, Maurer M. Successful treatment of cholinergic urticaria with anti-immunoglobulin E therapy. Allergy 2008;**63**:247–249.
57. Boyce JA. Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE. J Allergy Clin Immunol 2006;**117**:1415–1418.
58. Guzelbey O, Ardelean E, Magerl M, Zuberbier T, Maurer M, Metz M. Successful treatment of solar urticaria with anti-immunoglobulin E therapy. Allergy 2008;**63**:1563–1565.
59. Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. J Allergy Clin Immunol 2008;**122**:569–573.
60. Magerl M, Philipp S, Manasterski M, Friedrich M, Maurer M. Successful treatment of delayed pressure urticaria with anti-TNF-alpha. J Allergy Clin Immunol 2007;**119**:752–754.
61. O'Donnell BF, Barr RM, Black AK, Francis DM, Kermani F, Niimi N et al. Intravenous immunoglobulin in autoimmune chronic urticaria. Br J Dermatol 1998;**138**:101–106.
62. Dawn G, Urcelay M, Ah-Weng A, O'Neill SM, Douglas WS. Effect of high-dose intravenous immunoglobulin in delayed pressure urticaria. Br J Dermatol 2003;**149**: 836–840.
63. Pereira C, Tavares B, Carrapatoso I, Loureiro G, Faria E, Machado D et al. Low-dose intravenous gammaglobulin in the treatment of severe autoimmune urticaria. Eur Ann Allergy Clin Immunol 2007;**39**: 237–242.
64. Thormann J, Laurberg G, Zachariae H. Oral sodium cromoglycate in chronic urticaria. Allergy 1980;**35**:139–141.
65. Laurberg G. Tranexamic acid (Cyklokapron) in chronic urticaria: a double-blind study. Acta Derm Venereol 1977;**57**:369–370.
66. Lawlor F, Ormerod AD, Greaves MW. Calcium antagonist in the treatment of symptomatic dermographism. Low-dose and high-dose studies with nifedipine. Dermatologica 1988;**177**: 287–291.
67. Lawlor F, Black AK, Ward AM, Morris R, Greaves MW. Delayed pressure urticaria, objective evaluation of a variable disease using a dermographometer and assessment of treatment using colchicine. Br J Dermatol 1989;**120**:403–408.
68. Dover JS, Black AK, Ward AM, Greaves MW. Delayed pressure urticaria. Clinical features, laboratory investigations, and response to therapy of 44 patients. J Am Acad Dermatol 1988;**18**:1289–1298.
69. Weber-Schoendorfer C, Schaefer C. The safety of cetirizine during pregnancy. A prospective observational cohort study. Reprod Toxicol 2008;**26**:19–23.
70. Schwarz EB, Moretti ME, Nayak S, Koren G. Risk of hypospadias in offspring of women using loratadine during pregnancy: a systematic review and meta-analysis. Drug Saf 2008;**31**: 775–788.
71. Simons FE. Prevention of acute urticaria in young children with atopic dermatitis. J Allergy Clin Immunol 2001;**107**:703–706.
72. Pollack CV Jr, Romano TJ. Outpatient management of acute urticaria: the role of prednisone. Ann Emerg Med 1995;**26**:547–551.
73. Watson NT, Weiss EL, Harter PM. Famotidine in the treatment of acute urticaria. Clin Exp Dermatol 2000;**25**:186–189.
74. Pontasch MJ, White LJ, Bradford JC. Oral agents in the management of urticaria: patient perception of effectiveness and level of satisfaction with treatment. Ann Pharmacother 1993;**27**:730–731.
75. Moscati RM, Moore GP. Comparison of cimetidine and diphenhydramine in the treatment of acute urticaria. Ann Emerg Med 1990;**19**:12–15.
76. Camarasa JM, Aliaga A, Fernandez-Vozmediano JM, Fonseca E, Iglesias L, Tagarro I. Azelastine tablets in the treatment of chronic idiopathic urticaria. Phase iii, randomised, double-blind, placebo and active controlled multicentric clinical trial. Skin Pharmacol Appl Skin Physiol 2001;**14**: 77–86.
77. Henz BM, Metzenauer P, O'Keefe E, Zuberbier T. Differential effects of new-generation H1-receptor antagonists in pruritic dermatoses. Allergy 1998;**53**:180–183.
78. La Rosa M, Leonardi S, Marchese G, Corrias A, Barberio G, Oggiano N et al. Double-blind multicenter study on the efficacy and tolerability of cetirizine compared with oxatomide in chronic idiopathic urticaria in preschool children. Ann Allergy Asthma Immunol 2001;**87**:48–53.
79. Handa S, Dogra S, Kumar B. Comparative efficacy of cetirizine and fexofenadine in the treatment of chronic idiopathic urticaria. J Dermatolog Treat 2004;**15**:55–57.
80. Lambert D, Hantzperg M, Danglas P, Bloom M. Double-blind comparative study of terfenadine and cetirizine in chronic idiopathic urticaria. Allerg Immunol (Paris) 1993;**25**:235–240.
81. Breneman DL. Cetirizine versus hydroxyzine and placebo in chronic idiopathic urticaria. Ann Pharmacother 1996;**30**:1075–1079.
82. Breneman D, Bronsky EA, Bruce S, Kalivas JT, Klein GL, Roth HL et al. Cetirizine and astemizole therapy for chronic idiopathic urticaria: a double-blind, placebo-controlled, comparative trial. J Am Acad Dermatol 1995;**33**:192–198.
83. Andri L, Senna GE, Betteli C, Givanni S, Andri G, Lombardi C et al. A comparison of the efficacy of cetirizine and terfenadine. A double-blind, controlled study of chronic idiopathic urticaria. Allergy 1993;**48**:358–365.
84. Goh CL, Wong WK, Lim J. Cetirizine vs placebo in chronic idiopathic urticaria—a double blind randomised cross-over study. Ann Acad Med Singapore 1991;**20**:328–330.
85. Juhlin L. Cetirizine in the treatment of chronic urticaria. Clin Ther 1991;**13**:81–86.
86. Alomar A, De La C, Fernandez J. Cetirizine vs astemizole in the treatment of chronic idiopathic urticaria. J Int Med Res 1990;**18**:358–365.
87. Kalivas J, Breneman D, Tharp M, Bruce S, Bigby M. Urticaria: clinical efficacy of cetirizine in comparison with hydroxyzine and placebo. J Allergy Clin Immunol 1990;**86**: 1014–1018.
88. Juhlin L, Arendt C. Treatment of chronic urticaria with cetirizine dihydrochloride a non-sedating antihistamine. Br J Dermatol 1988;**119**: 67–71.

89. Monroe E, Finn A, Patel P, Guerrero R, Ratner P, Bernstein D. Efficacy and safety of desloratadine 5 mg once daily in the treatment of chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. J Am Acad Dermatol 2003;**48**:535–541.
90. Monroe EW. Desloratidine for the treatment of chronic urticaria. Skin Therapy Lett 2002;**7**:1–2.
91. Ring J, Hein R, Gauger A, Bronsky E, Miller B. Once-daily desloratadine improves the signs and symptoms of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. Int J Dermatol 2001;**40**:72–76.
92. Kalis B. Double-blind multicentre comparative study of ebastine, terfenadine and placebo in the treatment of chronic idiopathic urticaria in adults. Drugs 1996;**52**(Suppl. 1):30–34.
93. Peyri J, Vidal J, Marron J. Ebastine in chronic urticaria: a double-blind placebo controlled study. J Dermatolog Treat 1991;**2**:51–53.
94. Degonda M, Pichler WJ, Bircher A, Helbling A. Chronic idiopathic urticaria: effectiveness of fexofenadine. A double-blind, placebo controlled study with 21 patients. Praxis (Bern 1994) 2002;**91**:637–643.
95. Kawashima M, Harada S, Tango T. Review of fexofenadine in the treatment of chronic idiopathic urticaria. Int J Dermatol 2002;**41**:701–706.
96. Kawashima M, Harada S. Efficacy and safety of fexofenadine HCl in japanese patients with chronic idiopathic urticaria. Int Arch Allergy Immunol 2001;**124**:343–345.
97. Nelson HS, Reynolds R, Mason J. Fexofenadine HCl is safe and effective for treatment of chronic idiopathic urticaria. Ann Allergy Asthma Immunol 2000;**84**:517–522.
98. Thompson AK, Finn AF, Schoenwetter WF. Effect of 60 mg twice-daily fexofenadine HCl on quality of life, work and classroom productivity, and regular activity in patients with chronic idiopathic urticaria. J Am Acad Dermatol 2000;**43**:24–30.
99. Kapp A, Pichler WJ. Levocetirizine is an effective treatment in patients suffering from chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled, parallel, multicenter study. Int J Dermatol 2006;**45**:469–474.
100. Kapp A, Wedi B. Chronic urticaria: clinical aspects and focus on a new antihistamine, levocetirizine. J Drugs Dermatol 2004;**3**:632–639.
101. Monroe EW. Relative efficacy and safety of loratadine, hydroxyzine, and placebo in chronic idiopathic urticaria and atopic dermatitis. Clin Ther 1992;**14**:17–21.
102. Belaich S, Bruttmann G, DeGreef H, Lachapelle JM, Paul E, Pedrali P et al. Comparative effects of loratadine and terfenadine in the treatment of chronic idiopathic urticaria. Ann Allergy 1990;**64**:191–194.
103. Monroe EW, Fox RW, Green AW, Izuno GT, Bernstein DI, Pleskow WW et al. Efficacy and safety of loratadine (10 mg once daily) in the management of idiopathic chronic urticaria. J Am Acad Dermatol 1988;**19**: 138–139.
104. Kapp A, Guinnepain M, Lachapelle J, Murietta-Aguttes M. Mizolastine in the treatment of chronic urticaria: a European clinical experience with 2452 patients managed in daily practice (PANEOS CU Study). In: Marone G, editor. Clinical immunology and allergy in medicine. Naples: JGC Editions, 2003.
105. Leynadier F, Duarte-Risselin C, Murrieta M. Comparative therapeutic effect and safety of mizolastine and loratadine in chronic idiopathic urticaria. URTILOR study group. Eur J Dermatol 2000;**10**:205–211.
106. Lorette G, Giannetti A, Pereira RS, Leynadier F, Murrieta-Aguttes M. One-year treatment of chronic urticaria with mizolastine: efficacy and safety. URTOL study group. J Eur Acad Dermatol Venereol 2000;**14**: 83–90.
107. Dubertret L, Murrieta Aguttes M, Tonet J. Efficacy and safety of mizolastine 10 mg in a placebo-controlled comparison with loratadine in chronic idiopathic urticaria: results of the MILOR Study. J Eur Acad Dermatol Venereol 1999;**12**: 16–24.
108. Ring J, Brockow K, Ollert M, Engst R. Antihistamines in urticaria. Clin Exp Allergy 1999;**29**(Suppl. 1): 31–37.
109. Lachapelle JM, Tennstedt D, Murietta M. Comparative efficacy and safety of mizolastine 10mg o.d. versus placebo in chronic idiopathic urticaria. Allergy 1998; **53**:s42.
110. Brostoff J, Fitzharris P, Dunmore C, Theron M, Blondin P. Efficacy of mizolastine, a new antihistamine, compared with placebo in the treatment of chronic idiopathic urticaria. Allergy 1996;**51**:320–325.
111. Gimenez-Arnau A, Pujol RM, Ianosi S, Kaszuba A, Malbran A, Poop G et al. Rupatadine in the treatment of chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled multicentre study. Allergy 2007;**62**:539–546.
112. Dubertret L, Zalupca L, Cristodoulo T, Benea V, Medina I, Fantin S et al. Once-daily rupatadine improves the symptoms of chronic idiopathic urticaria: a randomised, double-blind, placebo-controlled study. Eur J Dermatol 2007;**17**:223–228.
113. Siebenhaar F, Degener F, Zuberbier T, Martus P, Maurer M. High-dose desloratadine decreases wheal volume and improves cold provocation thresholds compared with standard-dose treatment in patients with acquired cold urticaria: a randomized, placebo-controlled, crossover study. J Allergy Clin Immunol 2009;**123**:672–679.
114. Serhat Inaloz H, Ozturk S, Akcali C, Kirtak N, Tarakcioglu M. Low-dose and short-term cyclosporine treatment in patients with chronic idiopathic urticaria: a clinical and immunological evaluation. J Dermatol 2008;**35**:276–282.
115. Bleehen SS, Thomas SE, Greaves MW, Newton J, Kennedy CT, Hindley F et al. Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multi-centre randomized double-blind study. Br J Dermatol 1987;**117**:81–88.
116. Diller G, Orfanos CE. Management of idiopathic urticaria with H1 + H2 antagonists. A crossover double blind long-term study. Z Hautkr 1983;**58**:785–793.
117. Harvey RP, Wegs J, Schocket AL. A controlled trial of therapy in chronic urticaria. J Allergy Clin Immunol 1981;**68**:262–266.
118. Monroe EW, Cohen SH, Kalbfleisch J, Schulz CI. Combined H1 and H2 antihistamine therapy in chronic urticaria. Arch Dermatol 1981;**117**: 404–407.
119. Goldsobel AB, Rohr AS, Siegel SC, Spector SL, Katz RM, Rachelefsky GS et al. Efficacy of doxepin in the treatment of chronic idiopathic urticaria. J Allergy Clin Immunol 1986;**78**:867–873.
120. Greene SL, Reed CE, Schroeter AL. Double-blind crossover study comparing doxepin with diphenhydramine for the treatment of chronic urticaria. J Am Acad Dermatol 1985;**12**:669–675.
121. Harto A, Sendagorta E, Ledo A. Doxepin in the treatment of chronic urticaria. Dermatologica 1985;**170**:90–93.

122. Kamide R, Niimura M, Ueda H, Imamura S, Yamamoto S, Yoshida H et al. Clinical evaluation of ketotifen for chronic urticaria: multicenter double-blind comparative study with clemastine. Ann Allergy 1989;**62**:322–325.
123. Reeves GE, Boyle MJ, Bonfield J, Dobson P, Loewenthal M. Impact of hydroxychloroquine therapy on chronic urticaria: chronic autoimmune urticaria study and evaluation. Intern Med J 2004;**34**:182–186.
124. Engin B, Ozdemir M. Prospective randomized non-blinded clinical trial on the use of dapsone plus antihistamine vs. antihistamine in patients with chronic idiopathic urticaria. J Eur Acad Dermatol Venereol 2008;**22**: 481–486.
125. Cassano N, D'Argento V, Filotico R, Vena GA. Low-dose dapsone in chronic idiopathic urticaria: preliminary results of an open study. Acta Derm Venereol 2005;**85**:254–255.
126. Kozel MM, Sabroe RA. Chronic urticaria: aetiology, management and current and future treatment options. Drugs 2004;**64**:2515–2536.
127. Kaplan AP. Chronic urticaria. Possible causes, suggested treatment alternatives. Postgrad Med 1983;**74**:209–215.
128. Kaplan AP. Urticaria: the relationship of duration of lesion to pathogenesis. Allergy Proc 1990;**11**:15–18.
129. Parsad D, Pandhi R, Juneja A. Stanozolol in chronic urticaria: a double blind, placebo controlled trial. J Dermatol 2001;**28**:299–302.
130. Bagenstose SE, Levin L, Bernstein JA. The addition of zafirlukast to cetirizine improves the treatment of chronic urticaria in patients with positive autologous serum skin test results. J Allergy Clin Immunol 2004;**113**:134–140.
131. Shahar E, Bergman R, Guttman-Yassky E, Pollack S. Treatment of severe chronic idiopathic urticaria with oral mycophenolate mofetil in patients not responding to antihistamines and/or corticosteroids. Int J Dermatol 2006;**45**:1224–1227.
132. Sands MF, Blume JW, Schwartz SA. Successful treatment of 3 patients with recurrent idiopathic angioedema with omalizumab. J Allergy Clin Immunol 2007;**120**:979–981.
133. Godse KV. Omalizumab in severe chronic urticaria. Indian J Dermatol Venereol Leprol 2008;**74**:157–158.
134. Dreyfus DH. Observations on the mechanism of omalizumab as a steroid-sparing agent in autoimmune or chronic idiopathic urticaria and angioedema. Ann Allergy Asthma Immunol 2008;**100**:624–625.
135. Beck HI, Cramers M, Herlin T, Sondergaard I, Zachariae H. Comparison of oxatomide and clemastine in the treatment of chronic urticaria. A double blind study. Dermatologica 1985;**171**:49–51.
136. Demaubeuge J, Tennstedt D, Broux R. Does mast cell protection plus mediator antagonism surpass the effect of a classic antihistaminic in the treatment of chronic urticaria? A double-blind comparison of oxatomide and mequitazine Dermatologica 1982;**164**:386–394.
137. Peremans W, Mertens RL, Morias J, Campaert H. Oxatomide in the treatment of chronic urticaria. A double-blind placebo-controlled trial. Dermatologica 1981;**162**:42–50.
138. Bressler RB, Sowell K, Huston DP. Therapy of chronic idiopathic urticaria with nifedipine: demonstration of beneficial effect in a double-blinded, placebo-controlled, crossover trial. J Allergy Clin Immunol 1989;**83**:756–763.
139. Parslew R, Pryce D, Ashworth J, Friedmann PS. Warfarin treatment of chronic idiopathic urticaria and angio-oedema. Clin Exp Allergy 2000;**30**:1161–1165.
140. Barlow RJ, Greaves MW. Warfarin in the treatment of chronic urticaria/angio-edema. Br J Dermatol 1992;**126**:415–416.
141. Czarnetzki BM, Algermissen B, Jeep S, Haas N, Nurnberg W, Muller K et al. Interferon treatment of patients with chronic urticaria and mastocytosis. J Am Acad Dermatol 1994;**30**: 500–501.
142. Torrelo A, Harto A, Ledo A. Interferon therapy for chronic urticaria. J Am Acad Dermatol 1995;**32**: 684–685.
143. Grattan CE. Histamine-releasing autoantibodies in chronic urticaria. Skin Pharmacol 1991;**4** (Suppl. 1): 64–70.
144. Bajaj AK, Saraswat A, Upadhyay A, Damisetty R, Dhar S. Autologous serum therapy in chronic urticaria: old wine in a new bottle. Indian J Dermatol Venereol Leprol 2008;**74**:109–113.
145. Staubach P, Onnen K, Vonend A, Metz M, Siebenhaar F, Tschentscher I et al. Autologous whole blood injections to patients with chronic urticaria and a positive autologous serum skin test: a placebo-controlled trial. Dermatology 2006;**212**:150–159.
146. Sharpe GR, Shuster S. The effect of cetirizine on symptoms and wealing in dermographic urticaria. Br J Dermatol 1993;**129**:580–583.
147. Magerl M, Schmolke J, Metz M, Zuberbier T, Siebenhaar F, Maurer M. Prevention of signs and symptoms of dermographic urticaria by single-dose ebastine 20 mg. Clin Exp Dermatol 2009;**34**:e137–e140.
148. Cap JP, Schwanitz HJ, Czarnetzki BM. Effect of ketotifen in urticaria factitia and urticaria cholinergica in a cross-over double-blind trial. Hautarzt 1985;**36**:509–511.
149. Kontou-Fili K, Maniatakou G, Demaka P, Gonianakis M, Palaiologos G, Aroni K. Therapeutic effects of cetirizine in delayed pressure urticaria: clinicopathologic findings. J Am Acad Dermatol 1991;**24**: 1090–1093.
150. Nettis E, Pannofino A, Cavallo E, Ferrannini A, Tursi A. Efficacy of montelukast, in combination with loratadine, in the treatment of delayed pressure urticaria. J Allergy Clin Immunol 2003;**112**: 212–213.
151. Vena GA, D'Argento V, Cassano N, Mastrolonardo M. Sequential therapy with nimesulide and ketotifen in delayed pressure urticaria. Acta Derm Venereol 1998;**78**: 304–305.
152. Barlow RJ, Macdonald DM, Black AK, Greaves MW. The effects of topical corticosteroids on delayed pressure urticaria. Arch Dermatol Res 1995;**287**:285–288.
153. Vena GA, Cassano N, D'Argento V, Milani M. Clobetasol propionate 0.05% in a novel foam formulation is safe and effective in the short-term treatment of patients with delayed pressure urticaria: a randomized, double-blind, placebo-controlled trial. Br J Dermatol 2006;**154**: 353–356.
154. Engler RJ, Squire E, Benson P. Chronic sulfasalazine therapy in the treatment of delayed pressure urticaria and angioedema. Ann Allergy Asthma Immunol 1995;**74**: 155–159.
155. Juhlin L. Inhibition of cold urticaria by desloratadine. J Dermatolog Treat 2004;**15**:51–59.
156. Bonadonna P, Lombardi C, Senna G, Canonica GW, Passalacqua G. Treatment of acquired cold urticaria with cetirizine and zafirlukast in combination. J Am Acad Dermatol 2003;**49**:714–716.
157. Dubertret L, Pecquet C, Murrieta-Aguttes M, Leynadier F. Mizolastine in primary acquired cold urticaria. J Am Acad Dermatol 2003;**48**:578–583.

158. Villas Martinez F, Contreras FJ, Lopez Cazana JM, Lopez Serrano MC, Martinez Alzamora F. A comparison of new nonsedating and classical antihistamines in the treatment of primary acquired cold urticaria (ACU). J Investig Allergol Clin Immunol 1992;**2**:258–262.
159. Magerl M, Schmolke J, Siebenhaar F, Zuberbier T, Metz M, Maurer M. Acquired cold urticaria symptoms can be safely prevented by ebastine. Allergy 2007;**62**:1465–1468.
160. Moller A, Henning M, Zuberbier T, Czarnetzki-Henz BM. Epidemiology and clinical aspects of cold urticaria. Hautarzt 1996;**47**: 510–514.
161. Wanderer AA, St Pierre JP, Ellis EF. Primary acquired cold urticaria. Double-blind comparative study of treatment with cyproheptadine, chlorpheniramine, and placebo. Arch Dermatol 1977;**113**: 1375–1377.
162. St-Pierre JP, Kobric M, Rackham A. Effect of ketotifen treatment on cold-induced urticaria. Ann Allergy 1985;**55**:840–843.
163. Riccioni G, Di Ilio C, Conti P, Theoharides TC, D'Orazio N. Advances in therapy with antileukotriene drugs. Ann Clin Lab Sci 2004;**34**: 379–387.
164. Hani N, Hartmann K, Casper C, Peters T, Schneider LA, Hunzelmann N et al. Improvement of cold urticaria by treatment with the leukotriene receptor antagonist montelukast. Acta Derm Venereol 2000; **80**:229.
165. Roelandts R. Diagnosis and treatment of solar urticaria. Dermatol Ther 2003;**16**:52–56.
166. Bilsland D, Ferguson J. A comparison of cetirizine and terfenadine in the management of solar urticaria. Photodermatol Photoimmunol Photomed 1991;**8**:62–64.
167. Hudson-Peacock MJ, Farr PM, Diffey BL, Goodship TH. Combined treatment of solar urticaria with plasmapheresis and PUVA. Br J Dermatol 1993;**128**:440–442.
168. Mang R, Stege H, Budde MA, Ruzicka T, Krutmann J. Successful treatment of solar urticaria by extracorporeal photochemotherapy (photopheresis)—a case report. Photodermatol Photoimmunol Photomed 2002;**18**:196–198.
169. Bissonnette R, Buskard N, McLean DI, Lui H. Treatment of refractory solar urticaria with plasma exchange. J Cutan Med Surg 1999;**3**:236–238.
170. Correia I, Silva J, Filipe P, Gomes M. Solar urticaria treated successfully with intravenous high-dose immunoglobulin: a case report. Photodermatol Photoimmunol Photomed 2008;**24**:330–331.
171. Maksimovic L, Fremont G, Jeanmougin M, Dubertret L, Viguier M. Solar urticaria successfully treated with intravenous immunoglobulins. Dermatology 2009;**218**:252–254.
172. Zuberbier T, Aberer W, Burtin B, Rihoux JP, Czarnetzki BM. Efficacy of cetirizine in cholinergic urticaria. Acta Derm Venereol 1995;**75**:147–149.
173. Zuberbier T, Althaus C, Chantraine-Hess S, Czarnetzki BM. Prevalence of cholinergic urticaria in young adults. J Am Acad Dermatol 1994;**31**:978–981.
174. Wong E, Eftekhari N, Greaves MW, Ward AM. Beneficial effects of danazol on symptoms and laboratory changes in cholinergic urticaria. Br J Dermatol 1987;**116**:553–556.
175. Spangler DL, Vanderpool GE, Carroll MS, Tinkelman DG. Terbutaline in the treatment of chronic urticaria. Ann Allergy 1980;**45**:246–247.
176. Di Lorenzo G, Pacor ML, Mansueto P, Esposito Pellitteri M, Lo Bianco C, Ditta V et al. Randomized placebo-controlled trial comparing desloratadine and montelukast in monotherapy and desloratadine plus montelukast in combined therapy for chronic idiopathic urticaria. J Allergy Clin Immunol 2004;**114**:619–625.
177. Reimers A, Pichler C, Helbling A, Pichler WJ, Yawalkar N. Zafirlukast has no beneficial effects in the treatment of chronic urticaria. Clin Exp Allergy 2002;**32**:1763–1768.
178. Sharpe GR, Shuster S. In dermographic urticaria H2 receptor antagonists have a small but therapeutically irrelevant additional effect compared with H1 antagonists alone. Br J Dermatol 1993;**129**:575–579.
179. Matthews CN, Boss JM, Warin RP, Storari F. The effect of H1 and H2 histamine antagonists on symptomatic dermographism. Br J Dermatol 1979;**101**:57–61.

Appendix

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

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

