Position paper

EAACI/GA²LEN/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/GA²LEN/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 (GA²LEN), 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).

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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, GA²LEN, 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,

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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.

Figure 1. Recommended treatment algorithm for chronic urticaria.
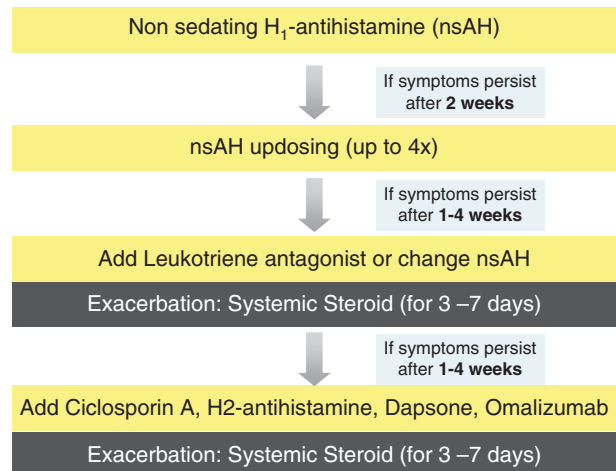
Comments on procedure on algorithm for chronic urticaria

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

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 ns sg H_1 and H_2-AH Cimetidine	High Very low	All weak	(28, 50, 114) (115–118)
					Monotherapy Tricyclic antidepressants (doxepin) Ketotifen Hydroxychloroquine Dapsone Sulfasalazine Methotrexate Corticosteroids	Low Low Very low Very low Very low Very low Very low		(119–121) (122) (123) (124, 125) (126) (126) (127, 128)
					Other treatment options Combination therapy ns sg H_1-AH and stanazolol ns sg H_1-AH and zafirlukast ns sg H_1-AH and Mycophenolate mofetil ns sg H_1-AH and narrowband UV-B ns sg H_1-AH and omalizumab	Low Very low Very low Very low Very low		(129) (130) (131) (51) (55, 59, 132–134)
					Monotherapy Oxatomide Nifedipine Warfarin Interferon Plasmapheresis Immunoglobulins Autologs whole blood Injection (ASST positive only)	Very low Very low Very low Very low Very low Very low (63) Very low (144, 145)		(135–137) (138) (139, 140) (141, 142) (26, 143)
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) Narrowband UV-B therapy	Very low Very low	All weak	(148) (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 Sulfasalazine	Very low Very low		(152, 153) (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 Increase dose up to four-fold	High	Strong	(113, 155–159) (113)	Trial with penicillin i.m./p.o. Trial with doxycyline p.o. Induction of physical tolerance.	Very low Very low	All weak	(160) (160) (160)
					Other treatment options Cyproheptadine Ketotifen Montelukast	Very low Low Very low		(41, 161) (162) (163, 164)
Solar urticaria	ns H$_1$-AH	Very low	Weak	(165, 166)	Induction of physical tolerance *Other treatment options* Plasmapheresis + PUVA Photopheresis Plasma exchange IVIGs Omalizumab	Very low Very low Very low Very low Very low Very low	All weak	(36) (167) (168) (169) (170, 171) (58)
d. Special types of inducible urticaria Cholinergic urticaria	ns H$_1$-AH – Increase dosage if necessary	Low Low	Weak	(172) (173)	'Exercise tolerance' *Other treatment options* Ketotifen Danazol Omalizumab	Very low Very low Very low Very low	All weak	(148) (174) (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).

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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/	Addition of H_2-AH to SedatingH_1-AH or nonsedating H_1-AH	Very low	All strong	(178, 179)
Urticaria factitia	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.

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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)

Zuberbier et al.

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)