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REVIEW ARTICLE

Urticaria: Current Opinions about Etiology, Diagnosis and Therapy

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In the last few decades an increasing understanding of the pathomechanisms involved in urticaria has highlighted the heterogeneity of different subtypes. According to the new European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum (EAACI/GA²LEN/EDF) guidelines, urticaria subtypes can be grouped into spontaneous urticaria, which includes acute urticaria and chronic urticaria, the physical urticarias, and other urticaria disorders, including, for example, contact urticaria. Clarity of nomenclature is required not only to choose the correct measures in diagnosis and management, but also to compare data from different studies. Urticaria has a profound impact on quality of life and performance. Effective treatment is thus required in all cases where avoidance of eliciting factors is not feasible. For symptomatic relief, non-sedating H1-antihistamines are the first choice in most subtypes of urticaria; however, double-blind controlled studies have shown that the dosages required may exceed those recommended for other diseases, e.g. allergic rhinitis. The current guidelines therefore suggest increasing the dosage up to fourfold, whereas alternative treatments should be reserved as add-on therapy for unresponsive patients. *Key words: urticaria; definition; pathogenesis; therapy.*

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Urticaria was described by Hippocrates, but it is only recently that the many different subtypes have been classified. In the last few years many of the molecular mechanisms involved in its pathogenesis have been discovered and there is growing evidence for heterogeneity of urticaria. This new knowledge requires an individual approach, which is important since the impairment of quality of life in urticaria is often high (1, 2).

This review has considered published studies up to September 2006 [Medline Search] and includes the suggestions of the European Academy of Allergology and Clinical Immunology (EAACI) position paper on physical urticaria (3), the guideline on urticaria by the British Association of Dermatologists (4) and the most recent European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum (EAACI/GA²LEN/EDF) guidelines. For preparing the latter, more than 300 specialists from over 15 countries held a consensus meeting regarding the definition, classification, routine diagnosis and management of urticaria. Evidence-based suggestions, prepared by a panel in advance, were discussed using a voting system (5, 6).

Due to the heterogeneity of the disease, the interpretation of divergent data from different centres regarding eliciting causes in subtypes of urticaria and their therapeutic responsiveness is, however, sometimes difficult, as the influence of different study populations is considerable.

DEFINITION AND CLASSIFICATION

Urticaria is characterized by the rapid appearance of wheals and/or angioedema. A wheal consists of three typical features: (*i*) a central swelling of variable size; (*ii*) an associated itching or sometimes burning; and (*iii*) a fleeting duration of usually 1–24 h. Angioedema is defined as a sudden, pronounced swelling of the lower dermis and subcutis. It is sometimes painful and resolution is slower than for wheals (up to 72 h).

Classification

The clinical manifestations of different urticaria subtypes vary considerably. Also, it is important to note that in one patient two or more different subtypes of urticaria can coexist. Table I presents a classification for clinical use. Physical urticarias, although of a chronic nature, are grouped separately, since they depend on the presence of their eliciting physical factors, whereas in acute and chronic urticaria wheals arise spontaneously without specific external physical stimuli.

Disease activity

Another important factor in classifying urticaria is disease activity. Where physical triggers are implicated, an exact measurement of the intensity of the eliciting factor can be made, e.g. the temperature. For spontaneous urticaria, assessing disease activity is more complex. The new guidelines propose a unified scoring system that will facilitate comparison of study results

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Table I. *Classification of urticaria*

Group/Subgroup	Characteristics
Spontaneous urticaria	*Definition*
Acute urticaria	Spontaneous wheals < 6 weeks
Chronic urticaria	Spontaneous wheals > 6 weeks
Physical urticaria	*Eliciting factors*
Acquired cold urticaria	Cold air/water/wind/food/objects
Delayed pressure urticaria	Vertical pressure (wheals arising with a 3–8 h latency)
Heat urticaria	Localized heat
Solar urticaria	UV and/or visible light
Dermographic urticaria/urticaria factitia/	Mechanical shearing forces (wheals arising after 1–5 min)
Vibratory urticaria/angioedema	Vibratory forces, e.g. pneumatic hammer
Other urticaria disorders	
Aquagenic urticaria	Water
Cholinergic urticaria	Increase of body temperature
Contact urticaria	Contact with urticariogenic substance
Exercise-induced anaphylaxis/ urticaria	Physical exercise

UV: ultraviolet

from different centres. This simple scoring system (Table II) is based on the assessment of key urticaria symptoms (wheals and pruritus). This simple instrument is also suitable for evaluation of disease activity by patients with urticaria and their treating physicians. The self-evaluation of the last 24 h each day by the patient has proven to be very robust and helpful since disease activity often varies during the day.

Quality of life

The health-related quality of life (HRQoL) parameter is presently recognized as a primary outcome in clinical trials, population studies and public health.

While HRQoL has been assessed extensively in numerous dermatological conditions, few studies have evaluated this topic in patients with chronic urticaria.

Recently, a questionnaire specifically developed for chronic urticaria has been validated. This new tool, the Chronic Urticaria Quality of Life Questionnaire (CU-Q2OL), assesses physical, emotional, social and practical aspects of quality of life that characterize this condition (7).

SUBTYPES OF URTICARIA

Spontaneous urticaria

Acute urticaria. The lifetime prevalence of acute urticaria ranges from 12% to 15% (8, 9) or even 23.5% (10). In a prospective study, in a rural area of Brandenburg, Germany, a 1-year incidence of 0.154% was found, which equals a lifetime prevalence of 12.32% based on a life expectancy of 80 years (11). However, mild

Table II. *Assessment of disease activity in patients with spontaneous urticaria*

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

Sum of score: (0–6).

symptoms may not have been reported and the true lifetime prevalence must be estimated as 15–20%.

Regarding aetiology, the above-mentioned prospective study in acute urticaria showed that although 63% of the patients suspected food to be the cause, in only 1 of 109 patients food was shown to be the causing agent upon thorough investigation, which shows that patient history, especially in acute urticaria, may be misleading (12).

Drugs can elicit acute urticaria both as allergens (e.g. penicillin) and as pseudoallergens (e.g. non-steroidal anti-inflammatory drugs (NSAIDs)).

The most frequent reason for acute urticaria, however, appears to be viral infections of the upper respiratory tract. However, in some patients only combinations of viral infections (increasing mast cell reactivity) and NSAID intake elicit urticaria.

Chronic urticaria. Due to the lack of cross-sectional studies, there is no reliable data regarding the prevalence of chronic urticaria; it is estimated at 1%. As in acute urticaria, type I – allergic reactions are only rarely responsible for the development of chronic urticaria (13, 14). For different subsets of patients with chronic urticaria, pseudoallergic reactions against food and food additives have repeatedly been discussed in the past, as have infections and autoreactive mechanisms.

Our own results (14) show that in those patients improving on a diet low in pseudoallergens, 30% show a decrease in symptoms only after 10–14 days on the diet. The study included unselected patients with chronic continuous urticaria, who had not previously received a diagnostic work-up. Approximately 50% of the responders did not express total clearance of symptoms, pointing at other possible co-factors involved in the pathogenesis. These results were confirmed by Pigatto & Valsecchi (15), who investigated a group of 202 patients with chronic urticaria using the same diet. In this study 126 patients improved on the diet, whereas 35 patients did not show any benefit from the diet and 41 patients dropped out. In both studies reactions to food additives were seen in only a minority of patients (19% and 37%, respectively), and meanwhile the relevance of naturally occurring pseudoallergens, especially aromatic compounds found in vegetables and wine, have been confirmed (16).

Various studies have investigated the occurrence of anti-FcεRI-α-autoantibodies, which have been described to be of pathophysiological relevance in some patients with urticaria and disease course is more pronounced in those affected (17–19). These autoantibodies were found in the same frequency as described earlier, but they could be found in both patients with idiopathic chronic urticaria (7/22) as well as in patients with pseudoallergy against food whose symptoms cleared on elimination diet (6/17) (20). In addition, it has been shown that these autoantibodies cross-link the IgE-receptor if it is not occupied by IgE, which is rarely the case under physiological conditions (21, 22). There are two possible explanations for these findings. First, the FcεRI-α-autoantibodies are not of pathophysiological relevance in all patients with urticaria, and secondly, a synergism between the autoantibodies and other eliciting stimuli, e.g. food, is necessary for the appearance of clinical symptoms in some patients. Further research is necessary.

Apart from anti-IgE receptor autoantibodies, thyroid autoantibodies are also apparently associated with chronic urticaria (23), although the pathomechanism is unclear.

Also, infections have been associated with chronic urticaria. These include viral infections, e.g. hepatitis A and B, bacterial infections, e.g. of the nasopharynx or *Helicobacter pylori* of the gastrointestinal tract (24), which should be treated appropriately. The role of *H. pylori* infections as a possible cause of chronic urticaria was confirmed by some studies and a recent meta-analysis (25–27).

Parasites, a rare cause of urticaria in North European countries, but more frequent in other regions, should be eliminated. In the past, intestinal candidosis has been regarded as a highly important eliciting factor for chronic urticaria (9), but recent findings fail to support a significant causative role (12). Nevertheless, it is recommended that massive candidosis should be treated. In general, the frequency and relevance of infectious diseases as cause for chronic urticaria varies between different patient groups and in different regions. For example, hepatitis virus infections are a more frequent cause for chronic urticaria in southern Europe but a rare cause in northern Europe.

In addition to infections, non-infectious chronic inflammatory processes have also been identified to cause urticaria in some patients. These are particularly gastritis, reflux oesophagitis, inflammation of the bile duct or bile gland (12, 28), or rarely autoimmune disorders, e.g. systemic lupus erythematosus (SLE) and neoplasia.

Physical urticaria

Prevalence. The prevalence of the physical urticarias varies in the literature. One reason for this is the fact that they depend on the strength of the physical stimulus. Thus, Henz and co-workers (29) have shown that in normal subjects, 44.6% can react with an urticarial dermographism if a considerably increased pressure is used for testing. Under daily life-conditions, however, these subjects do not show any signs of urticaria. The same holds for the incidence of acquired cold urticaria (ACU), which is more frequent in a colder climate.

Dermographic urticaria factitia. Dermographic urticaria (synonym: urticaria) is defined by whealing induced by shearing forces on the skin. The wheals mostly appear rapidly, and associated pruritus is intense. Dermographic urticaria is the most frequent form of physical urticaria, affecting mainly young adults and has a mean duration of 6.5 years.

Delayed pressure urticaria. In contrast to dermographic urticaria, the typical lesions in this type of urticaria are deep, painful swellings developing 4–8 h after exposure to a vertical static pressure, persisting for 8–48 h, especially on the palms and soles. In delayed pressure urticaria, men are two times more frequently affected than women. The average age of onset is 30 years, the mean duration is 6–9 years.

Since pressure is the force per area, it is important to advise the patient that simple measures, such as avoiding sharp edges or using gel-filled soles in the shoes, can be helpful and effective in avoiding the outset of symptoms.

Acquired cold urticaria. ACU is defined as an urticarial reaction to exposure to cold, or more precisely: a sudden drop in skin temperature. Nine different subtypes have been described, including immediate and late reaction, localized cold urticaria as well as subtypes with generalized responses also in areas of skin not directly exposed to cold. While firm cold bodies or cold water can elicit cold urticaria in a majority of patients, in some patients only cold air will provoke symptoms.

ACU is more frequent in women than in men, affecting mainly young adults, with a mean duration of the disease of 4.2 years.

In a vast majority of patients with cold urticaria, the disease is idiopathic. However, the disease can also occur due to infections, neoplasia, or autoimmune disease. Specifically unrecognized bacterial infections have to be discussed, since in an open study 20–50% of patients with idiopathic ACU responded to antibiotic treatment (30).

Heat urticaria. Heat urticaria, different from cholinergic urticaria, which is elicited by an increase in the body core temperature, is a rare form of physical urticaria induced by direct contact of the skin with warm objects or warm air (31). The eliciting temperature ranges from 38°C to more than 50°C.

Solar urticaria. In solar urticaria wheals are elicited by light of wavelengths ranging between 280 and 760 nm. For individual patients the eliciting wavelength varies, but ultraviolet (UV) light is usually responsible.

As in other urticaria subtypes, women are affected more frequently and the disease usually starts in young adulthood. Leenutaphong et al. (32) have demonstrated that serum factors acting as IgE-dependent photo-allergens may be involved in the pathogenesis. Areas of the body that are constantly exposed to sunlight, such as the face and hands, are frequently not involved, due to photohardening, and this can be used therapeutically (33).

Vibratory angioedema. Vibratory angioedema is a rare condition in which strong vibrating mechanical forces, e.g. working with a pneumatic hammer, induce angioedema. Only a few case reports have been published, so epidemiological data is not available (34).

Other urticaria disorders

Cholinergic urticaria and exercise-induced urticaria. In contrast to the elicitation of symptoms through external stimuli in physical urticaria, lesions in cholinergic urticaria are due to a brief increase of the body core temperature. The most frequent reasons are passive warmth, e.g. hot bath (69%), sweating (56%), physical exercise (47%) and emotional distress (20%). Rarely, warm or spicy food (9% and 2%, respectively) or alcoholic beverages (9%) can also induce a brief rise in body core temperature (35).

The typical clinical picture is of pin-sized wheals surrounded by an erythema, but larger wheals can occur.

Cholinergic urticaria is frequent in young adults, with a prevalence of 11.2% in the age group 16–35 years (35). In the majority of cases symptoms are mild and 80% of affected persons do not seek medical advice for the condition. However, some patients are severely affected, with symptoms occurring, for example, after even a short walk. Systemic symptoms, including dizziness, nausea and headache, are observed in up to 11% of the patients. The main differential diagnosis includes exercise-induced anaphylaxis/urticaria, in which urticaria symptoms can also be induced by exercise, but not by passively increasing the body temperature.

Contact urticaria. Contact urticaria is defined by the appearance of wheals at sites where chemical substances have come into contact with the skin. The disease can be strictly confined to the areas of contact, but generalized systemic symptoms can occur, especially in IgE-mediated allergic contact urticaria.

Common eliciting factors include food, plants, drugs, cosmetics, industrial chemicals, animal product and textiles.

Aquagenic urticaria. This rare type of urticaria needs to be differentiated from contact urticaria due to the fact that water is not itself the causative agent, but probably liberates a water-soluble allergen from the stratum corneum, which then acts as an allergen.

The disease is five times more frequent in females than males, with an average onset in young adulthood. The lesions resemble those of cholinergic urticaria with mostly pin-sized wheals on the trunk.

DIAGNOSIS OF URTICARIA

Due to the heterogeneity of the disease with its many subtypes, guidelines for diagnosis can only cover a routine programme. In all guidelines intense and costly general screening programmes for urticaria are not suggested.

Diagnosis should comprise a thorough history and physical examination, and the use of basic laboratory tests to rule out severe systemic disease. Specific provocation and laboratory tests should be carried out on an individual basis, to investigate the suspected cause.

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

- Time of onset of disease
- Frequency and duration of wheals
- Diurnal variation
- Shape, size, and distribution of wheals
- Associated angioedema
- Associated subjective symptoms of lesion, e.g. itch, pain
- Family history regarding urticaria, atopy
- Previous or current allergies, infections, internal diseases, or other possible causes
- Induction by physical agents or exercise
- Use of drugs (NSAIDs, injections, immunizations, hormones, laxatives, suppositories, ear and eye drops, and alternative remedies)
- Food
- Smoking habits
- Type of work
- Hobbies
- Occurrence in relation to weekends, holidays, and foreign travel
- Surgical implantations
- Reactions to insect stings
- Relationship to the menstrual cycle
- Response to therapy
- Stress
- Quality of life related to urticaria

The second step is physical examination of the patient. This should include a test for dermographism. Ideally, if acceptable to the patient, antihistamine therapy should be discontinued for at least 2–3 days and immunosuppressive therapy for at least one week, but tests for physical urticaria can also be helpful to define thresholds in treated patients with only partial remission.

Subsequent diagnostic steps depend on the nature of the urticaria subtype, as summarized in Table III. In physical urticaria subtypes the determination of thresholds is very important, e.g. for cold urticaria a very convenient Peltier effect-based temperature test has been developed (36).

While in some countries, e.g. Scandinavia, a commercial basophil release test is offered, currently the only generally available test to screen for autoantibodies against the IgE receptor is the autologous serum skin test. This needs to be performed with utmost care since infections could be transmitted, particularly if patients are not injected with their own serum, by mistake.

Furthermore, for the diagnosis of urticaria it must always be remembered that in one patient different subtypes of urticaria can coexist, e.g. chronic urticaria and dermographic urticaria. It may thus happen that diagnosis reveals an eliciting cause for one of the subtypes, which then goes into remission after the appropriate treatment, while the other subtype remains unchanged.

MANAGEMENT

Although the subtypes of urticaria are elicited by a great diversity of factors, treatment mainly follows some basic principles. These are:

- Identification and elimination of underlying causes (where applicable)
- Avoidance or elimination of the eliciting stimulus
- Inhibition of mast cell mediators

Identification and elimination of underlying causes

Removal of infectious agents and treatment of inflammatory processes. In physical urticaria infections as a cause are found only in few cases of acquired cold and dermographic urticaria, but, as described above, chronic urticaria appears more often to be associated with a variety of inflammatory or infectious processes.

Removal of FcεRI autoantibodies.There is currently no advised routine treatment of chronic urticaria by removal of autoantibodies. Although plasmapheresis has been shown to be of temporary benefit in individual, severely affected patients (37), this is too costly and invasive for routine purposes. This is also true for other agents inhibiting antibody formation, such as cyclosporine (38–41) or high-dose immunoglobulin infusions (42).

Dietary management. IgE-mediated food allergy is rare in urticaria (11, 12), but in a subgroup of patients with chronic urticaria pseudoallergic reactions to naturally occurring food ingredients and, in some cases, to food additives are seen (11, 12, 43). 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 of at least 3–6 months. During this time spontaneous 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 as relevant allergens are rapidly eliminated, whereas in

Table III. Recommended diagnostic tests in frequent urticaria subtypes (modified according to Zuberbier et al. (5))

Group/Subgroup	Routine diagnostic tests	Extended diagnostic programme[a]
Spontaneous urticaria		
Acute urticaria	None[b]	None[b]
Chronic urticaria	Differential blood count and ESR/CRP[c], omission of suspected drugs (e.g. NSAID)	Test for infectious diseases (e.g. Helicobacter pylori) and type I allergy, autoantibodies, thyroid hormones, physical tests, pseudoallergen-free diet for 3 weeks, autologous serum skin test, serum tryptase, skin biopsy
Physical urticaria		
Acquired cold urticaria	Cold provocation and threshold test (ice cube, cold water, cold wind, TEMPtest)	Differential blood count and ESR/CRP[c], cryoproteins, rule out other diseases, especially infections
Delayed pressure urticaria	Pressure test (0.2–1.5 kg/cm^2 for 10 and 20 min)	None
Heat urticaria	Heat provocation and threshold test (warm water)	None
Solar urticaria	UV and visible light of different wavelengths	Rule out other light-induced dermatoses
Dermographic urticaria/urticaria factitia	Elicit dermographism	Differential blood count, ESR/CRP
Other urticaria disorders		
Aquagenic urticaria	Wet cloths at body temperature applied for 20 min	None
Cholinergic urticaria	Exercise and hot bath provocation	None
Contact urticaria	Prick/ECT test read after 20 min	None
Exercise-induced anaphylaxis/urticaria	According to history exercise test with/without food	None

[a]Depending on suspected cause; [b]unless strongly suggested by patient history, e.g. allergy; [c]as indication of severe systemic disease.
ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NSAID: non-steroidal anti-inflammatory drug; ANA: antinuclear antibodies; UV: ultraviolet; ECT: epicutaneous test.

pseudoallergy a diet has often to be maintained for 2–3 weeks before beneficial effects can be observed. Diet is usually not helpful in subtypes of urticaria other than chronic continuous urticaria.

Avoidance of eliciting stimuli

For this therapeutic approach, an exact diagnosis is a basic prerequisite.

Drugs. Suspected agents should be omitted entirely or substituted for by another class of drugs. In particular, drugs causing pseudoallergic reactions (the prototype being aspirin and other NSAIDs) can both elicit urticaria as well as aggravate pre-existing chronic urticaria.

Physical stimuli. Detailed information about the physical properties of the respective stimulus and the threshold helps to control exposure in daily life.

Stress. Approximately 50% of all patients with chronic urticaria report that stress is a trigger for the onset of symptoms. Strategies aimed at avoiding this unspecific stimulus have proven to be helpful in reducing disease activity and improving quality of life.

Inhibition of mast cell mediators

Almost all symptoms of urticaria are mediated mainly by H_1-receptors. The development of second-generation non-sedating or low-sedating antihistamines has largely improved the quality of life of patients with urticaria. In addition, new generation antihistamines should be preferred, since they also exert anti-inflammatory effects, such as inhibition of cytokine release from basophils and mast cells (49, 50). The effect of antihistamines in urticaria is dose-dependent (51, 52) and higher dosages are usually well tolerated, but care must be taken, since side-effects such as sedation can occur more frequently in some cases at higher dosages. Apart from terfenadine and astemizole, which should no longer be used due to the danger of cardiac side-effects, second-generation antihistamines, having a good safety profile, must be considered as first-line symptomatic treatment for urticaria. Increasing the dosage up to four-fold is advised since this has less side-effects than alternative treatment (6, 53).

Further progress with regard to drug safety was achieved by the development of the new generation antihistamines, e.g. desloratadine, fexofenadine and levocetirizine, most which are metabolites of earlier antihistamines. The highest reported accidental overdosage of antihistamine (50-fold of the prescribed dosage of cetirizine in an 18-month-old boy) induced no adverse effects (54). The main drug interactions have been described for the old sedating antihistamines in association with drugs affecting the central nervous system, like analgesics, hypnotics, sedatives and mood elevating drugs as well as alcohol. Monoamine oxidase inhibitors can prolong and intensify anticholinergic effects. With the exception of cetirizine, desloratadine, fexofenadine and levocetirizine, other modern antihistamines are also metabolized in the liver (55). This can lead to increased plasma levels when there is concomitant treatment with drugs employing the same enzyme system for metabolism, for example ketoconazole or erythromycin.

In summary, considering their good safety profile, second-generation antihistamines must be considered as first-line symptomatic treatment for urticaria (level of evidence 1^{++}, grade of recommendation A (Table IV).

Although efficient systemic corticosteroids should be avoided for long-term treatment, since dosages necessary to suppress symptoms are usually high with obligatory side-effects. Cyclosporin A also has a moderate, direct effect on mast cell mediator release (44), but is reserved for alternative treatment due to high costs.

Psoralen ultraviolet A therapy (PUVA) reduces the numbers of mast cells and has been used successfully in mastocytosis (45, 46). UV-A and UV-B has also been studied as additive treatment in urticaria (47, 48).

Further therapeutic possibilities

Alternative treatments are needed for patients who are unresponsive to higher dosages of antihistamines. Since the side-effects of many of these substances are considerable, it may be wise to try to use them as add-on therapy only in patients unresponsive to antihistamines.

Table IV summarizes the current standard drug treatment and alternatives in several subtypes of urticaria.

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

CONCLUSION

Urticaria severely affects quality of life. Disease management should be prompt and requires close cooperation with the patient. An individual approach is necessary due to the complexity of the disease. Management is based on the avoidance of triggering factors, treatment of associated diseases and symptomatic pharmacological treatment. For the last, symptoms are controlled in the majority of patients by new generation antihistamines, which have a very low adverse effect profile and can be used at higher dosages in non-responding patients. Alternative treatment should be considered only for unresponsive patients.

Table IV. *Effective treatment in urticaria recommended by the majority of a panel and the audience (modified according to Zuberbier et al. (6))*

Type of urticaria	Standard treatment	Methodological quality[a]	Level of evidence[b]	Grade of recommendation[c]	Treatment for non-responsive patients	Methodological quality[a]	Level of evidence[b]	Grade of recommendation[c]
Acute urticaria	*ns sg H1-AH*:		2–	D	Prednisone, 2×20 mg/day for 4 days	+	2^{+}	D
	Loratadine	–	2–	D	Prednisolone, 50 mg /day for 3 days	–	2^{-}	D
	Cetirizine	–	2–	D	H2-blocker, single dose or 5 days	+	2^{-}	D
Chronic urticaria	*ns sg H1-AH*:		1^{++}	A	*Combination therapy*:			
	Azelastine	+	1^{-}		ns sg H_1-AH and cyclosporin A	++	2^{++}	C
	Cetirizine	++	1^{+}		ns sg H_1-AH and montelukast	+	2^{-}	D
	Desloratadine	++	1^{+}		ns sg H_1 and H_2–AH cimetidine	+	2^{-}	D
	Ebastine	+	1^{-}		*Monotherapy:*			
	Fexofenadine	++	1^{+}		Tricyclic antidepressants (doxepin)	+	2^{+}	D
	Levocetirizine	++	1^{+}		Ketotifen	++	2^{++}	C
	Loratadine	++	1^{+}		Hydroxychloroquine	–	2^{-}	D
	Mizolastine	++	1^{+}		Dapsone	No RCT	3	D
	– Increase dosage if necessary		3	C	Sulfasalazine	No RCT	3	D
					Methotrexate	No RCT	3	D
					Corticosteroids	No RCT	4	D
					Other treatment options:			
					Combination therapy:			
					ns sg H_1-AH and stanazolol	++	2^{+}	D
					ns sg H_1-AH and zafirlukast	–	2^{-}	D
					Monotherapy:			
					Oxatomide	–	2^{-}	D
					Nifedipine	–	2^{-}	D
					Montelukast	–	2^{-}	D
					Warfarin	–	2^{-}	D
					Interferon	No RCT	3	D
					Plasmapheresis	No RCT	3	D
					Immunoglobulins	No RCT	3	D
					Azathioprine			
					Climate therapy			
					UV light treatment			
Dermographic urticaria/ urticaria factitia	*ns sg H1-AH*:		2^{-}	D	Ketotifen	+	2^{-}	D
	Cetirizine	+	2^{+}	D	(see also chronic urticaria)			
Delayed pressure urticaria	*ns sg H1-AH*:		2^{-}	D	*Combination therapy:*			
	Cetirizine	–	2^{-}	D	Montelukast and ns H1-AH (loratadine)	+	2^{-}	D
	High-dose ns H_1-AH	no RCT	3–4	D	*Monotherapy:*			
					Prednisone 40–20 mg	–	2^{-}	D
					Dapsone	No RCT	3	D
					Other treatment options			
					Combination therapy:			
					Ketotifen and nimesulide	–	2^{-}	D
					Monotherapy:			
					Clobetasol prop.05% Ointment	+	2^{-}	D
					Methotrexate	No RCT	3	D
					Sulfasalazine	No RCT	3	D

Table IV continued

Acquired cold urticaria	*ns sg H1-AH*:	++	2^+	B	Trial with penicillin i.m./p.o.	No RCT	3	D
	Loratadine				Trial with doxycyline p.o.	No RCT	3	D
	Cetirizine				Induction of physical tolerance			
	Mizolastine				**Other treatment options:**			
	Desloratadine				Cyproheptadine	+	2^-	D
					Ketotifen	+	2^+	D
					Montelukast	No RCT	3	D
Solar urticaria	*ns sg H1-AH:*			D	Induction of physical tolerance			
	Cetirizine	–	2^-	D	Cyclosporine A		3	D
	Fexofenadine		3	D	**Other treatment options**:			
	Loratadine		3	D	Plasmapheresis		3	D
					Plasmapheresis + PUVA		3	D
					Photopheresis		3	D
					Plasma exchange		3	D
					IVIgs		3	D
					Hydroxychloroquine		4	D
Cholinergic urticaria	*ns sg H1-AH*:			D	”Exercise tolerance”			
	Cetirizine	+	2	D	**Other treatment options:**			
	– Increase dosage if necessary	++	2^+	D	Ketotifen	+	2^-	D
					Danazol	+	2^-	D

[a]Rating of methodological quality of the study or review according to the Metholodogy Checklist 2: Randomized Controlled Trials (RCT) of the Scottish Intercollegiate Guidelines Network (SIGN); ++, All or most of the criteria have been fulfilled. Where they have not been fulfilled, the conclusions of the study or review are thought very unlikely to alter; +, Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or adequately described are thought unlikely to alter the conclusions;), Few or no criteria have been fulfilled. The conclusions of the study are thought likely or very likely to alter; [c]The grade of recommendation according to SIGN criteria; 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-control or cohort or studies. High quality case-control 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 control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal; 2^-, Case control 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; [b]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 Metholodogy Checklist 2: Randomized Controlled Trials of the Scottish Intercollegiate Guidelines Network (SIGN). A, At least one meta analysis, systematic review, or RCT rated as 1^{++}, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1^+, directly applicable to the target population, and demonstrating overall consistency of results; B, A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1^{++} or 1^+; C, A body of evidence including studies rated as 2^+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2^{++}; D, Evidence level 3 or 4; or extrapolated evidence from studies rated as 2^+.

ns sg H_1-AH: non-sedating second-generation H_1-antihistamines; PUVA: psoralen ultraviolet A therapy; IVIgs: intravenous immunoglobulins.

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