A Summary of the New International *EAACI/GA²LEN/EDF/WAO Guidelines* in Urticaria

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Abstract: Urticaria is a heterogeneous group of disorders, especially acute urticaria and angiooedema can be a medical emergency. This paper summarizes the *EAACI/GA²LEN/EDF/WAO guidelines*, the most recent international guidelines from 2009. Patients with urticaria are often not diagnosed and treated appropriately and the guidelines state that clinicians should always aim to provide complete symptom relief. The mainstay of urticaria treatment is the use of modern nonsedating antihistamines, if required up to 4-fold of standard doses.

Key Words: urticaria, acute urticaria, guidelines, nonsedating antihistamines

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Urticaria is a common, heterogeneous group of disorders with a large variety of underlying causes. It is characterized by the appearance of fleeting wheals, which each last 1–24 hours and/or angioedema lasting up to 72 hours. This paper summarizes the *EAACI/GA²LEN/EDF/WAO guidelines* from 2009[1,2] for an outline of the diagnosis and treatment of the disease. Currently, these are the only international guidelines available. These guidelines are the result of a consensus reached during a panel discussion at the 3rd International Consensus Meeting on Urticaria, *Urticaria 2008*, a joint initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the EU-funded network of excellence, the Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF), and the World Allergy Organization (WAO).

CLASSIFICATION OF URTICARIA ON THE BASIS OF ITS DURATION, FREQUENCY, AND CAUSES

The spectrum of clinical manifestations of different urticaria subtypes is very wide. Additionally, 2 or more different subtypes of urticaria can coexist in any given patient. Table 1 presents a classification for clinical use.

Another important factor the new guidelines point out is assessing disease activity. Where physical triggers are implicated an exact measurement of the intensity of the eliciting factor can be made, for example, the temperature and duration of application in cold urticaria or pressure, and the duration of application until provocation of lesions in delayed pressure urticaria. For nonphysical acute and chronic urticaria, assessing disease activity is more complex. The

TABLE 1. Assessment of Disease Activity in Urticaria Patients

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

Sum of score: 0–6.

TABLE 2. Suggested Questions

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

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TABLE 3. Recommended Diagnostic Tests in Frequent Urticaria Subtypes

Types	Subtypes	Routine Diagnostic Tests (Recommended)	Extended Diagnostic Programme (Suggested) for Identification of Eliciting Factors and for Ruling Out Possible Differential Diagnoses if Indicated
Spontaneous urticaria	Acute spontaneous urticaria	None	None
	Chronic spontaneous urticaria	Differential blood count and ESR or CRP omission of suspected drugs (e.g. NSAID)	Test for (i) infectious diseases (e.g. Helicobacter pylon); (ii) type I allergy; (iii) functional autoantibodies; (iv) thyroid hormones and autoantibodies; (v) skin tests including physical tests; (vi) pseudoallergen-free diet for 3 weeks and tryptase, (vii) autologous serum skin test, lesional skin biopsy
Physical urticaria	Cold contact urticaria	Cold provocation and threshold test (ice cube, cold water, cold wind)	Differential blood count and ESR/CRP cryoproteins rule out other diseases, especially infections
	Delayed pressure urticaria	Pressure test (0.2–1.5 kg/cm² for 10 and 20 minutes)	None
	Heat contact urticaria	Heat provocation and threshold test (warm water)	None
	Solar urticaria	UV and visible light of different wave lengths	Rule out other light-induced dermatoses
	Demographic urticaria/ urticaria factitia	Elicit demographism	Differential blood count, ESR/CRP
Other urticaria types	Aquagenic urticaria	Wet cloths at body temperature applied for 20 minutes	None
	Cholinergic urticaria	Exercise and hot bath provocation	None
	Contact urticaria	Prick/patch test read after 20 minutes	None
	Exercise-induced anaphylaxis/urticaria	According to history exercise test with/without food but not after a hot bath	None

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NSAID, nonsteroidal anti-inflammatory drugs.
Depending on suspected cause.
Unless strongly suggested by patient history, e.g. allergy.
As indication of severe systemic disease.

guidelines propose using scales from 0 to 3. This simple scoring system (Table 1) is based on the assessment of key urticaria symptoms (wheals and pruritus). It is also suitable for evaluation of disease activity by urticaria patients and their treating physicians and it has been validated.[3]

As urticaria symptoms frequently change in intensity during the course of a day, overall disease activity is best measured by advising patients to document 24-hour self-evaluation scores for several days.

DIAGNOSIS OF URTICARIA

Because of the heterogeneity of urticaria and its many subtypes, guidelines for diagnosis might start with a routine patient evaluation, which should comprise a thorough history and physical examination, and the ruling out of severe systemic disease by basic laboratory tests. Specific provocation and laboratory tests should be carried out on an individualized basis on the basis of 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 suggested by the guidelines are summarized in Table 2.

The second step is physical examination of the patient. This should include a test for dermographism. Subsequent diagnostic steps will depend on the nature of the urticaria subtype, as summarized in Table 3.

TREATMENT OF URTICARIA

Omission of Eliciting Drugs

Common drugs eliciting and aggravating chronic spontaneous urticaria include nonsteroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors.[1,2] If

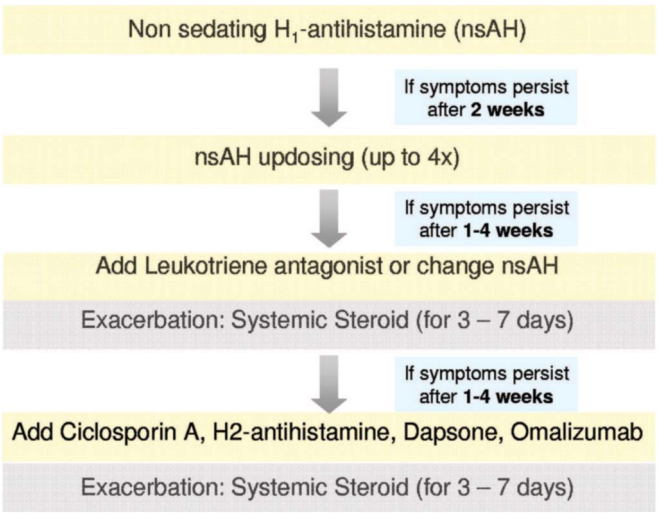

FIGURE 1. Taken from EAACI/GA²LEN/EDF/WAO Guideline: Management of Urticaria.

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TABLE 4. Modified From EAACI/GA²LEN/EDF/WAO Guideline: Management of Urticaria

Urticaria Subtype	Treatment	Quality of Evidence	Strength of Recommendation for Use of Intervention	Alternatives (for Patients Who Do Not Respond to Other Interventions)	Quality of Evidence	Strength of Recommendation for Use of Alternativeintervention
a. Acute spontaneous urticaria	ns sg H1-AH: l	Low	Strong	Prednisolone, 2 x 20 mg/d* for 4 days	Low	Weak
				Prednisolone, 50 mg/d* for 3 days	Very low	
				H2-blocker, single dose for 5 days	Very low	
b. Chronic spontaneous urticaria	ns sg H1-AH	High	Strong	ns sg H1-AH and ciclosporin	High	All weak
				ns sg H1 and H2-AH cimetidine	Very low	
	- Increase dosage if necessary up to fourfold	Low	Weak	***Monotherapy:***		
				Tricyclic antidepressants (doxepin)	Low	
				Ketotifen	Low	
				Hydroxychloroquine	Very low	
				Dapsone	Very low	
				Sulfasalazine	Very low	
				Methotrexate	Very low	
				Corticosteroids	Very low	
				Other treatment options		
				Combination therapy:		
				ns sg H1-AH and stanazolol	Low	
				ns sg H1-AH and zafirlukast	Very low	
				ns sg H1-AH and mycophenolate mofetil	Very low	
				ns sg H1-AH and narrowband UV-B	Very low	
				ns sg H1-AH and omalizumab	Very low	
				Monotherapy:		
				Oxatomide	Very low	
				Nifedipine	Very low	
				Warfarin	Very low	
				Interferon	Very low	
				Plasmapheresis	Very low	
				Immunoglobulins	Very low	
				Autologous whole blood injection (ASST positive only)	Very low	
c. Physical urticaria	In generel for physical urticarias: Avoidance of stimuli	High	Strong		Very low	
Symptomatic dermographism/ Urticaria factitia	ns sg H1-AH:	Low	Weak	Ketotifen (see also chronic urticaria) narrowband UV-B therapy	Very low	All weak
Delayed pressure urticaria	ns sg H1-AH: cetirizine	Low	All weak	***Combination therapy:***		All weak
				Montelukast and ns H1-AH (loratadine)	Very low	
	High dose ns H1-AH	Very low		***Monotherapy:***		
		Very low		Prednisolone 40–20 mg*	Very low	
				Other treatment options		
				Combination therapy:		
				Ketotifen and nimesulide	Very low	

(*Continued*)

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TABLE 4. (*Continued*)

Urticaria Subtype	Treatment	Quality of Evidence	Strength of Recommendation for Use of Intervention	Alternatives (for Patients Who Do Not Respond to Other Interventions)	Quality of Evidence	Strength of Recommendation for Use of Alternativeintervention
				Monotherapy:		
				Topical clobetasol propionate.	Very low	
				Sulfasalazine	Very low	
Cold urticaria	ns sg H1-AH	High	Strong	Trial with penicillin i.m./p.o.	Very low	All weak
				Trial with doxycyline p.o.	Very low	
	Increase dose up to fourfold			Induction of physical tolerance		
				Other treatment options		
				Cyproheptadine	Very low	
				Ketotifen	Low	
				Montelukast	Very low	
Solar urticaria	ns H1-AH	Very low	Weak	Induction of physical tolerance	Very low	All weak
				Other treatment options		
				Plasmapheresis + PUVA	Very low	
				Photopheresis	Very low	
				Plasma exchange	Very low	
				IVIGs	Very low	
				Omalizumab	Very low	
d. Special types of inducible urticaria						
Cholinergic urticaria	ns H1-AH	Low	Weak	"Exercise tolerance"	Very low	All weak
				Other treatment options		
	- Increase dosage if necessary, up to fourfold	Low		Ketotifen, danazol	Very low	
				Omalizumab	Very low	

drugs are suspected to cause or aggravate urticaria, they should be omitted or substituted appropriately.

Avoidance of Physical and Other Stimuli in Inducible Urticaria

In patients suffering from inducible urticaria such as cholinergic urticaria, solar urticaria, or cold urticaria, the avoidance of the trigger should be attempted as much as possible.

Treatment of Infectious Agents

In some cases of chronic spontaneous urticaria eradication of infections, such as *H. pylori*, bowel parasites and bacterial infections of the nasopharynx, have shown to provide a benefit in the management of the disease.[1,2,4,5] However, the eradication of intestinal candida is no longer believed to be of benefit. In addition chronic inflammatory processes such as gastritis, esophageal reflux disease and inflammations of the bile duct and gall bladder are now believed to be potential causative factors and should be managed accordingly.[2,6]

Dietary Modifications

If IgE-mediated food allergy has been identified as a trigger of chronic spontaneous urticaria, the specific allergen should be avoided as much as possible. This should clear the symptoms within 24 to 48 hours. Pseudoallergens can also elicit or aggravate chronic spontaneous urticaria but, in contrast to Typ-I allergens, need to be avoided for at least 3 to 6 months, to provide any benefit.

Symptomatic Treatment

The aim of the symptomatic therapy is to provide complete symptom relief. In general a stepwise approach is followed as illustrated in Figure 1.[2]

Nonsedating antihistamines have a very good evidence for efficacy, a very good safety profile and are low in cost.Increasing the dose of the second generation antihistamines is recommended because of a good safety profile, good evidence of efficacy, and low cost. Although the third treatment step is supported by the benefit of a good safety profile and low to medium-low cost, there is no or insufficient evidence for its efficacy in high quality RCTs. Corticosteroids should only be used in the treatment of acute urticaria or acute flares of chronic spontaneous urticaria. Their long-term use should be avoided outside specialist clinics. In patients with severe urticaria

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refractory to any of the above measures, ciclosporin can be used as it has an effect on mast-cell mediator release and prevents basophil histamin release. However, because of its medium-high costs, moderate safety, and moderate level of evidence of efficacy, its benefits need to be carefully balanced against the disadvantages. Another option is the use of Omalizumab (anti-IgE) in some cases of chronic spontaneous urticaria, cholinergic-, cold-, or solar urticaria. Its high cost and low level of evidence of efficacy should be carefully considered before introducing the medication. Furthermore, many other treatments have been proposed like dapsone, sulfasalazine, methotrexat, IVIG, interferon, and plasmapharesis but only been tested in uncontrolled trials or case studies and further studies are required to evaluate their effects. Table 4 illustrates the evidence for commonly used drugs.

SUMMARY

The new guidelines for urticaria give clear recommendations, on diagnosis and treatment. Further RCTs are required to provide the best possible treatment to patients, who do not respond to first-or second line-treatments.

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