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CONSENSUS STATEMENT ON THE MANAGEMENT OF URTICARIA

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Abstract

This consensus statement was developed by Special Interest Group – Urticaria (IADVL). Urticaria, a heterogeneous group of diseases, often cannot be recognized by its morphology. Due to non-specific and non-affordable diagnosis, management of urticaria, especially chronic urticaria, is very challenging. This guideline includes definition, causes, classification and management of urticaria. Urticaria has a profound impact on the quality of life and causes immense distress to patients, necessitating effective treatment. One approach to manage urticaria is identification and elimination of the underlying cause(s) and/or eliciting trigger(s), while the second one is treatment aimed at providing symptomatic relief. This guideline recommends use of second-generation non-sedating H1 antihistamines as the first-line treatment. The dose can be increased up to four times to meet the expected results. In case patients still do not respond, appropriate treatment options can be selected depending on the cost.

Keywords: *Chronic urticaria*, *consensus statement*, *definition*, *treatment*, *urticaria*

Introduction

Urticaria consists of a heterogeneous group of diseases. Development of urticarial skin lesions and/or angioedema, which is a common and distinctive skin reaction, is shared by all types and subtypes of urticaria. Other medical conditions may also have wheals and these conditions need to be differentiated from urticaria.[1]

Rapid appearance of wheals and/or angioedema is a characteristic of urticaria. A wheal is characterized by three typical features: (i) a central swelling of variable size, almost invariably surrounded by a reflex erythema, (ii) associated itching or sometimes burning sensation, and (iii) transient nature, with skin returning to its normal appearance usually within 1–24 hours.[1] Angioedema is associated with (i) sudden, pronounced swelling of lower dermis and subcutis; (ii) sometimes pain rather than itching; (iii) frequent involvement of mucous membranes; and (iv) resolution that is slower than for wheals and can take up to 72 hours.[1]

Though symptomatically urticaria may be seen as an allergic reaction, the disease is often autoimmune or idiopathic in nature.[2] Degranulation of mast cells and basophils by immunological or non-immunological mechanism is the final step in the pathogenesis of urticaria. Various pathways or mechanisms like IgE or IgE receptor pathway, complement system, arachidonic acid pathway, and direct mast cell degranulation are involved in the pathogenesis of urticaria.[3]

Frequency and Causes

Classification of the urticarial diseases is based on duration and frequency. The timeline of 6 weeks of daily or nearly daily symptoms has been chosen as the arbitrary dividing point between acute and chronic urticaria (CU). This classification has been useful for appropriate differential diagnosis, as common causes of acute and chronic urticaria are different and the two conditions behave differently.

Acute urticaria is more common in young adults and children and most often is caused by allergic reactions to food, drug, infection

(commonly viral), insect sting or transfusion. Sometimes patients seek confirmatory testing from a physician about a suspected food or drug trigger. If a particular medication is suspected which has limited therapeutic alternatives, an allergy evaluation may be sought. Some medication reactions may not be truly allergic but may be caused by nonspecific mast cell releasing or anaphylactoid properties of the drug. Common drugs with these properties include opiates, vancomycin, and radiocontrast media (especially high-osmolar or ionic agents). Other causes of acute urticarial reactions include sea food, allergy to insect envenomation, and transfusion reactions. A specific cause may not be identified in around 50% of cases of acute urticaria. Once symptoms have persisted on a frequent basis for more than 6 weeks, the patient is considered to have CU. The two largest subgroups of CU are physical urticarias, in which physical stimuli initiate the formation of lesions, and autoimmune urticaria, due to functional autoantibodies to the high affinity receptor for IgE (FcεRI) or less commonly to IgE itself.

Identification of specific cause is rare in CU compared to acute urticaria. It is equally important to find and eliminate the relevant physical or environmental triggers along with consideration of systemic conditions which are associated with urticaria.[4]

Around 15–20% of people have urticaria at least once during their lifetime. Though no age is bar for urticaria and/or angioedema, urticaria is seen most commonly after adolescence. The highest incidence of urticaria is seen in young adults. Exact epidemiology of CU in India is unknown. Worldwide it occurs in 0.1–3% of the population.[5] Women are twice commonly affected compared to men.

In a study from India, it was found that out of 500 cases of urticaria, 37% patients had physical urticaria[6] [Table 1].

Diagnosis of Urticaria

Detailed patient history along with physical examination and ruling out severe systemic disease by conducting basic laboratory tests should be considered for routine patient evaluation because of heterogeneity of urticaria and its multiple subtypes.[1]

Guidelines for Treatment of Chronic Spontaneous Urticaria (CU)

Urticaria has a profound impact on the quality of life and causes immense distress to patients, necessitating effective treatment.

The management of urticaria should consist of following two approaches and both lines of treatment should be considered in every patient.

1. Identification of underlying cause(s) and/or eliciting trigger(s)
2. Treatment for symptomatic relief

Especially for patients suffering from physical urticaria, treating the underlying cause is the most desirable; but it is unfortunately not possible in the most of the patients. Avoidance of the triggering factor or stimulus is the second best approach. This is possible for the rare patients with IgE-mediated urticaria and partly for patients suffering from physical urticaria.[7]

A step by step approach tailored to the individual patient should be taken for management of CU. Routine management of autoimmune and non-autoimmune CU is the same.[2]

General Measures

Aspirin is the commonest drug aggravating urticaria. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) can worsen CU in 20–30% of patients during active phase but probably not in remission.[8] A number of aggravating factors of urticaria can be avoided by simple measures. Treating physicians can identify these triggers or aggravating factors by taking careful history from the patient. The aggravating factors may include diet, drugs, alcohol, viral infections, local heat and friction, and mental stress.[9] In India, diet is often considered as a cause of any skin allergy. Patients often come to physician with a list of “not to eat” items. Pseudoallergens may be important cause of urticaria in some patients. Pseudoallergic reactions to additives, natural salicylates, and aromatic compounds are mostly dose related. At present, we do not know how much is to be ingested to precipitate an attack. In an earlier study by Zuberbier *et al*, only 19% of patients reacted severely to challenge capsules containing food additives.[10] Although there are no published studies on food items causing urticaria, in the clinical practice it has been observed that tomato, wine, herbs and nuts can worsen urticaria.

Overheating and local pressure because of belts and clothing may aggravate CU. Often there is an overlap between physical urticaria and CU. Urticaria may be worsened by alcohol because of the vasodilatation. Viral infections may also aggravate urticaria. Upregulation of cytokines with the acute phase response causing temporary state of enhanced mast cell releasability may be the underlying mechanism for aggravation of urticaria during viral infections.[9] Treatment of identifiable cause, avoidance of triggers, advice and written information about the condition, and antihistamines should be part of treatment plan. Soothing agents such as calamine lotion give excellent symptomatic relief.

Antihistamines

Antihistamines are the first line of treatment for all patients with CU. Classic H1 antihistamines which have the side effect of sedation include chlorpheniramine, hydroxyzine, diphenhydramine,[11] etc. Newer H1 antihistamines include fexofenadine, loratadine, desloratadine, cetirizine, levocetrizine, ebastine, mizolastine, olapatadine, rupatadine, etc. H2 antihistamines include ranitidine and famotidine. In some cases of CU, the addition of H2 antihistamines may prove effective.

First-generation antihistamines can interfere with rapid eye movement (REM) sleep and impact on learning and performance. New GA^{2}LEN/EDF/EAACI/WAO guidelines do not recommend the use of these sedating antihistamines for the routine management of CU as the first-line agents.[7] Second-generation antihistamines should be considered as the first-line symptomatic treatment for urticaria because of their good safety and tolerability profile.[7] Second-generation antihistamines in higher doses have been shown to be effective in control of chronic spontaneous urticaria. This has been verified in studies using even up to fourfold higher than recommended doses of desloratadine,[12] fexofenadine,[13] levocetirizine[14] and rupatadine.[15] Two long-term studies in healthy volunteers have demonstrated that fexofenadine, at doses up to 240 mg once daily for up to 12 months, is safe and well tolerated.[16] No dose-related increases in corrected QT interval (QTc) were found with fexofenadine doses up to 800 mg once daily or 690 mg twice daily for 28 days.[17] Fexofenadine does not lead to sedation at approved as well as supratherapeutic doses. Cetirizine has a potential to cause sedation at therapeutic as well as supratherapeutic dose, whereas levocetirizine and desloratadine may have the potential of sedative effect at supratherapeutic dose.[18]

Antihistamines up to four times than the recommended dosages control symptoms in the majority of patients with urticaria in general practice. For the remaining unresponsive patients, alternative treatments are required.[7]

- Presently, corticosteroids are commonly used in the management of allergic diseases. There is a strong recommendation from GA^{2}LEN/EDF/EAACI/WAO guidelines against the long-term use of corticosteroids outside specialist clinics if it can be avoided.[7] A dose of 0.5 mg/kg/day of prednisolone can be used for up to 1 week to resolve the resistant urticaria.
- Cyclosporine has a moderate, direct effect on mast cell mediator release.[19] It is recommended only for patients with severe disease refractory to maximum dose of antihistamines. It has much better risk/benefit ratio compared with steroids.[7] Many controlled studies have reported cyclosporine to be effective at the dose of 4–5 mg/kg. Low-dose (2–3 mg/kg) therapy has also shown its beneficial effect in controlling urticaria.[20] Generally, the duration of cyclosporine therapy is 3 months.
- Methotrexate may be a useful and cost-effective alternative for steroid-dependent CU in the Indian settings.[21] Functional autoantibodies do not correlate with the response to treatment. The beneficial effects seen with methotrexate are due to its anti-inflammatory and immunosuppressive properties. It can be used up to 10-15 mg/week for its steroid-sparing effect.[22]
- Omalizumab, a recombinant, humanized, monoclonal antibody acts as a neutralizing antibody by binding IgE at the same site on IgE as its high-affinity receptor; FcεRI. It reduces IgE serum levels and blocks the IgE attachment to mast cells and other immune cells, which prevents IgE-mediated inflammatory changes. It is approved for the treatment of moderate-to-severe persistent asthma in adults and adolescents older than 12 years of age who have a positive skin test to a perennial allergen. Dosing of omalizumab is based on weight and pretreatment serum IgE levels. It is administered via subcutaneous injection every 2–4 weeks. The most commonly reported adverse event with omalizumab is injection site reaction. It has now been shown to be dramatically effective in selected patients with chronic spontaneous urticaria.[23]
- Autologous serum therapy (AST) has been found to be successful in CU in an Indian study.[24] Larger studies are required to confirm findings.

A strong recommendation was made by the GA^{2}LEN/EDF/EAACI/WAO panel to discourage the use of first-generation antihistamines in infants and children. Thus, in children, the same first-line treatment and updosing (weight adjusted) is recommended as in adults.[7]

The GA^{2}LEN/EDF/EAACI/WAO panel suggests that in pregnant patients, the use of second-generation antihistamines should be limited to loratadine with the possible extrapolation to desloratadine.[7] As safety studies are not available, the increased dosage of second-generation antihistamines can only be carefully suggested in pregnancy. While using loratadine, it must be remembered that it is metabolized in the liver. First-generation antihistamines may be cautiously used in pregnancy when symptoms are nonresponsive to second-generation antihistamines.[7]

According to the data from Berlin Teratogen Information Service, 196 women exposed in any trimester (11% in the first trimester) showed no increased risk of birth defects or other adverse outcomes with cetirizine.[25] Use of loratadine, desloratadine, or fexofenadine in a therapeutic dose is less likely to cause an adverse effect in nursing infant because of the minimal exposure of a breast feeding infant to the drugs through breast milk.[26]

Safety of second-generation antihistamines should be considered when these drugs are to be used in patients with liver disease, renal impairment and in geriatric patients. Table 2 shows the metabolism and dose adjustment of various second-generation

antihistamines.[27]

Recommendations for combinations of non-sedating H1 antihistamines with H2 antihistamines or with antileukotrienes or dapsone are based on low levels of evidence [Figure 1].[7]

Conclusion

Urticaria has a profound impact on the quality of life and causes immense distress to patients, necessitating effective treatment. This guideline includes definition, causes, classification and management of urticaria. One approach to manage urticaria is identification and elimination of the underlying cause(s) and/or eliciting trigger(s), while the second is treatment aimed at providing symptomatic relief. We recommend use of second-generation non-sedating H1 antihistamines as the first-line treatment. The dose can be increased up to four times to meet the expected results. In case patients still do not respond, appropriate treatment options can be selected depending on the costs and risk/benefit ratios.

Disclaimer

The contents/recommendations in this consensus statement are recommendations only and are not absolute or binding on members. The principles outlined in this statement are of general nature, based on current evidence, and individual variations may occur from patient to patient, hence appropriate modifications may be needed depending on the needs of the given patient, as per the discretion of physician and as per emerging evidence in future. Each patient has to be treated on his/her merit and the ultimate judgment regarding the choice of treatment should be made by the physician, keeping in view the individual patient and training and experience of treating physician. The physician must exercise his judgment in light of all the circumstances of the individual patient. This statement is prepared with the sole purpose of establishing minimum standards of care and as a service to the members of IADVL. Neither the SIG Urticaria members nor IADVL will be held responsible either directly or indirectly for any legal claims.

About SIG urticaria

The SIG Urticaria was constituted as per the resolution of Annual General Body Meeting of IADVL members, 2010. The SIG-Urticaria group consisted of following members:

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Footnotes

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References

1. Zuberbier T, Asero R, Bindslev-Jensen C, Canonica GW, Church MK, Gimeénez-Arnau AM, et al. EAACI/GA[2]LEN/EDF/WAO guideline: Definition, classification and diagnosis of urticaria. *Allergy.* 2009;64:1417–26. [PubMed: 19772512]

2. Yadav S, Upadhyay A, Bajaj AK. Chronic urticaria: An overview. *Indian J Dermatol.* 2006;51:171–7.

3. Khandpur S, Dash S. Urticaria :Etiology and pathogenesis. In: Sharma VK, editor. *Handbook of urticaria.* First edition. New Delhi: 2008. pp. 7–11.

4. Dibbern DA, Jr, Dreskin SC. Urticaria and angioedema: an overview. *Immunol Allergy Clin N Am.* 2004;24:141–62.

5. Greaves MW. Chronic urticaria. *N Engl J Med.* 1995;332:1762–72.

6. Singh M, Kaur S, Kanwar AJ. Evaluation of the causes of physical urticarias. *Indian J Dermatol Venereol Leprol.* 1990;56:109–11.

7. Zuberbier T, Asero R, Bindslev-Jensen C, Canonica GW, Church MK, Gimeénez-Arnau AM, et al. EAACI/GA[2]LEN/EDF/WAO guideline: management of urticaria. *Allergy.* 2009;64:1427–43. [PubMed: 19772513]

8. Grattan CE. Aspirin sensitivity and urticaria. *Clin Exp Dermatol.* 2003;28:123–7. [PubMed: 12653694]

9. Grattan C. Chronic urticaria: General principles and management. In: Greaves MW, Kaplan AP, editors. *Urticaria and angioedema.* New York: Informa Healthcare; 2009. pp. 319–20.

10. Zuberbier T, Chantraine-Hess S, Hartmann K, Czarnetzki BM. Pseudoallergen free diet in the treatment of chronic urticaria. *Acta Derm Venereol.* 1995;75:484–7.

[PubMed: 8651031]

11. Godse KV. Chronic urticaria and treatment options. *Indian J Dermatol.* 2009;54:310–2. [PMCID: PMC2807703] [PubMed: 20101328]

12. Siebenhaar F, Degener F, Zuberbier T, Martus P, Maurer M. High-dose desloratadine decreases wheat volume and improves cold provocation thresholds as compared with standard dose treatment in patients with acquired cold urticaria: A randomized, placebo-controlled, crossover study. *J Allergy Clin Immunol.* 2009;123:672–9. [PubMed: 19201016]

13. Godse KV, Nadkarni NJ, Jani G, Ghate S. Fexofenadine in higher doses in chronic spontaneous urticaria. *Indian Dermatol Online J.* 2010;1:45–6.

14. Godse KV. Updosing of antihistamines to improve control of chronic urticaria. *Indian J Dermatol Venereol Leprol.* 2010;76:61–2. [PubMed: 20061736]

15. Gimenez-Arnau A, Izquierdo I, Maurer M. The use of a responder analysis to identify clinically meaningful differences in chronic urticaria patients following placebo-controlled treatment with rupatadine 10 and 20 mg. *J Eur Acad Dermatol Venereol.* 2009;23:1088–91. [PubMed: 19453774]

16. Nathan RA, Mason J, Bernstein DI, Howland WC, 3rd, Kaiser HB, Meltzer EO, et al. Long-Term Tolerability of Fexofenadine in Healthy Volunteers. *Clin Drug Invest.* 1999;18:317–28.

17. Pratt CM, Mason J, Russell T, Reynolds R, Ahlbrandt R. Cardiovascular Safety of Fexofenadine HCl. *Am J Cardiol.* 1999;83:1451–4. [PubMed: 10335761]

18. Smith SM, Gums JG. Fexofenadine: Biochemical, pharmacokinetic and pharmacodynamic properties and its unique role in allergic disorders. *Expert Opin Drug Metab Toxicol.* 2009;5:813–22. [PubMed: 19545214]

19. Stellato C, de Paulis A, Ciccarelli A, Cirillo R, Patella V, Casolaro V, et al. Anti-inflammatory effect of cyclosporine A on human skin mast cells. *J Invest Dermatol.* 1992;98:800–4. [PubMed: 1373749]

20. Kessel A, Toubi E. Cyclosporine-A in severe chronic urticaria: the option for long-term therapy. *Allergy.* 2010;65:1478–82. [PubMed: 20626384]

21. Godse K. Methotrexate in autoimmune urticaria. *Indian J Dermatol Venereol Leprol.* 2004;70:377. [PubMed: 17642672]

22. Perez A, Woods A, Gratten CE. Methotrexate: A useful steroid-sparing agent in recalcitrant chronic urticaria. *Br J Dermatol.* 2010;162:191–4. [PubMed: 19903174]

23. Godse KV. Omalizumab in severe chronic urticaria. *Indian J Dermatol Venereol Leprol.* 2008;74:157–8. [PubMed: 18388382]

24. Bajaj AK, Saraswat A, Upadhyay A, Damisetty R, Dhar S. Autologous serum therapy in chronic urticaria: Old wine in a new bottle. *Indian J Dermatol Venereol Leprol.* 2008;74:109–13. [PubMed: 18388366]

25. Weber-Schoendorfer C, Schaefer C. The safety of cetirizine during pregnancy.A prospective observational cohort study. *Reprod Toxicol.* 2008;26:19–23. [PubMed: 18571373]

26. So M, Bozzo P, Inoue M, Einarson A. Safety of antihistamines during pregnancy and lactation. *Can Fam Physician.* 2010;56:427–9. [PMCID: PMC2868610] [PubMed: 20463270]

27. Cuvillo A, Mullol J, Bartra J, Dávila I, Jáuregui I, Montoro J, et al. Comparative pharmacology of the H1 antihistamines. *J Investig Allergol Clin Immunol.* 2006;16(Supplement 1):3–12.

Figures and Tables

Table 1

Classification of urticaria subtypes (presenting with wheals and/or angioedema)*

Types	Subtypes	Definition
Spontaneous urticaria	Acute spontaneous urticaria	Spontaneous wheals and/or angioedema < 6 weeks
	Chronic spontaneous urticaria	Spontaneous wheals and/or angioedema > 6 weeks
Physical urticaria	Cold contact urticaria	Eliciting factor: cold objects/air/fluids/wind
	Delayed pressure urticaria	Eliciting factor: vertical pressure (wheals arising with a 3–12 hour latency)
	Solar urticaria	Eliciting factor: ultraviolet and/or visible light
	Urticaria factitia/dermographic urticaria	Eliciting factor: mechanical shearing forces (wheals arising after 1–5 min)
	Vibratory urticaria/angioedema	Eliciting factor: vibratory forces, e.g. pneumatic hammer
Other types of urticaria	Aquagenic urticaria	Eliciting factor: water
	Cholinergic urticaria	Elicitation by increase of body core temperature due to physical exercises, spicy food
	Exercise-induced anaphylaxis/urticaria	Eliciting factor: physical exercise

*Reference: Zuberbier T, Asero R, Bindslev-Jensen C, Canonica GW, Church MK, Gime´nez-Arnau AM, *et al*. EAACI/GA²LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. Allergy 2009;64:1417-26

Table 2

Metabolism and dose adjustment of various second-generation antihistamines

Drug	Liver metabolism	Dose adjustment
Fexofenadine	<8%	Kidney failure
Levocetrizine	<15%	Liver and kidney failure
Desloratadine	Yes	Liver and kidney failure
Rupatadine	Yes	Liver and kidney failure
Cetirizine	<40%	Liver and kidney failure
Loratadine	Yes	Liver and kidney failure

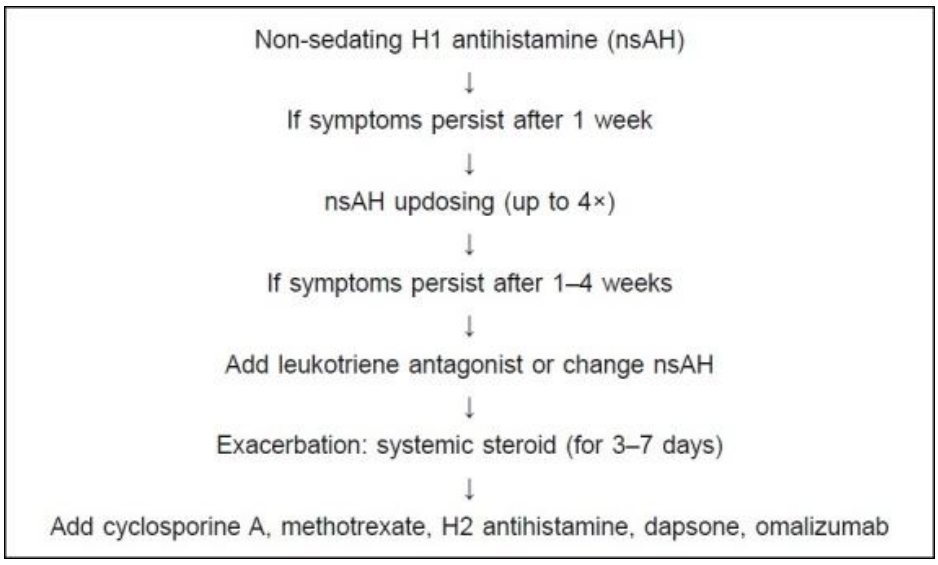


Figure 1

Management of chronic spontaneous urticaria

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