Abstract
This article is developed by the Skin Allergy Research Society of India for an updated evidence-based consensus statement for the management of urticaria, with a special reference to the Indian context. This guideline includes updated 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 by identification and elimination of the underlying cause(s) and/or eliciting trigger(s) while the second one is by treatment for providing symptomatic relief. This guideline recommends the use of second-generation nonsedating 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 associated medical condition, severity of the symptoms, affordability of the drugs, and accessibility of modern biologics such as omalizumab.

Key Words: Angioedema, antihistamine, autologous serum therapy, chronic urticaria, cyclosporine, hydroxyzine, Indian guidelines, methotrexate, montelukast, omalizumab

Definition
Urticaria or hives is a common skin condition that affects population with a lifetime prevalence of up to 22% and point prevalence of 1%. Hives consist of three typical features; central swelling of variable size, surrounding reflex erythema, and associated symptoms of pruritus or burning. It usually resolves within a few hours and always by 24 h. Urticaria may or may not be associated with angioedema. Angioedema is typically characterized by sudden, pronounced swelling of the lower dermis and subcutis. Sometimes, it is associated with pain rather than pruritus. It frequently involves the mucous membranes and may take up to 72 h for resolution. Often both urticaria and angioedema coexist as relapsing and remitting episodes.[1]

Modern Classification of Urticaria
Classification of urticaria is based on its episodic nature, i.e., acute or chronic along with further identifiable eliciting factors.
The aim of this guideline is to provide an updated definition and classification of urticaria and to provide evidence-based diagnostic and therapeutic approach in Indian perspective. This guideline has involved experts from different parts of India and had also taken into account variations in patients, medical systems, and access to diagnosis and treatment across the country.

### Epidemiology and Course of Urticaria

CSU is known to be the most common form of CU (66 to 93% of cases). Lifetime prevalence for urticaria is reported as 7.8–22.3%, with point prevalence being 0.5–1.0%.

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**Table 1: Classification of urticaria**

| Type                     | Subtype               | Definition                        |
|--------------------------|-----------------------|-----------------------------------|
| Spontaneous urticaria    | Acute spontaneous    | Wheals and/or angioedema <6 weeks |
|                          | Chronic spontaneous  | Wheals and/or angioedema >6 weeks |

| Type                     | Subtype               | Precipitating factor             |
|--------------------------|-----------------------|----------------------------------|
| Inducible urticaria      |                       |                                  |
| Physical urticaria       | Cold urticaria        | Cold objects, air, fluid, wind   |
|                         | Delayed pressure urticaria | Vertical pressure (wheals in 3-12 h) |
|                         | Heat urticaria        | Localised heat                   |
|                         | Solar urticaria       | UV, visible light                |
|                         | Dermographic urticaria| Mechanical shearing force (wheals in 1-5 min) |
|                         | Vibratory urticaria   | Vibratory forces, e.g., pneumatic hammer (wheals within 1-2 h) |
|                         | Aquagenic urticaria   | Water                            |
|                         | Cholinergic urticaria | Increasing core body temperature (due to exercise, spicy foods) |
|                         | Exercise-induced urticaria | Physical exercise               |
|                         | Contact urticaria     | Substance contact                |

UV: Ultraviolet

**Consensus statement 1**

Should the present classification be followed in urticaria?

There is strong recommendation to use this updated version of the classification.

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**Method of Preparing Urticaria Guideline**

As members of the panel of Skin Allergy Research Society of India, the authors had prepared in advance their suggestions regarding the definition, classification, diagnosis, and treatment of urticaria. The resulting draft of the guideline took into account all available evidence in the literature (including Medline and Google Scholar searches) and was based on the existing consensus papers of different associations around the globe [Table 2].

A structured questionnaire was prepared and consensus was finally achieved during consensus meeting at the annual skin allergy society meeting held on March 26, 2017, in Chennai. The participation of urticaria specialists from different states across India ensured that this consensus included regional differences in viewpoint. The expression “we recommend” was used for strong recommendations and “we suggest” for weak recommendations.

**Table 2: Existing consensus papers of different associations regarding the management of urticaria**

| Year | Name of the consensus paper                                      |
|------|------------------------------------------------------------------|
| 2014 | Argentine guidelines for urticaria and angioedema               |
| 2016 | Guideline of CU beyond                                          |
| 2013 | The EAACI/GA2LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: The 2013 revision and update[2] |
| 2007 | Guidelines for evaluation and management of urticaria in adults and children |
| 2012 | Japanese guidelines for diagnosis and treatment of urticaria in comparison with other countries |
| 2013 | Management of childhood urticaria: Current knowledge and practical recommendations |
| 2012 | Management of CU in Asia: 2010 AADV consensus guidelines         |
| 2014 | The diagnosis and management of acute and CU: 2014 update       |
| 2009 | EAACI/GA2LEN/EDF/WAO guideline: Management of urticaria         |

CU: Chronic urticaria

The aim of this guideline is to provide an updated definition and classification of urticaria and to provide evidence-based diagnostic and therapeutic approach in Indian perspective. This guideline has involved experts from different parts of India and had also taken into account variations in patients, medical systems, and access to diagnosis and treatment across the country.
Pathophysiology

The pathogenesis of CSU is yet to be fully characterised. It is thought to be mediated by aberrant release of histamine and other inflammatory mediators from mast cells and basophils.[1] CSU skin lesions show recruitment of mast cells and also basophils, neutrophils, eosinophils, and T lymphocytes.[6] It is now recognised that urticaria is a mast cell-driven disease. Activated mast cells release histamine and other mediators. These mediators activate sensory nerves. However, mast cell-activating signals in urticaria are ill-defined and likely to be heterogeneous and diverse.[3] Mast cell activation in CSU may either be through autoimmune, allergic, or idiopathic mechanisms.

Degranulation of mast cells releases histamine and other inflammatory mediators, such as platelet-activating factor and pro-inflammatory cytokines, which ultimately activates sensory nerves and elicits local vasodilatation, plasma extravasation as well as leukocyte trafficking to urticarial lesions.[4] The oedema of the upper and mid-dermis in wheals is due to dilatation of the postcapillary venules and lymphatic vessels beneath the upper dermis, whereas in angioedema, lower dermis and the subcutis are involved. The oedematous skin lesions often involve upregulation of endothelial cell adhesion molecules and perivascular infiltrate of neutrophils and/or eosinophils, macrophages, and T-cells.[6,9]

As IgE is a key to the release of histamine and other pro-inflammatory mediators from mast cells and basophils following degranulation, it may play a role in CSU. Specific IgG antibodies against the FccRIα subunit of IgE receptor also account for 30–50% of CU cases, and 5–10% of cases show IgG antibodies against IgE itself.[10,11] Most interestingly in some CU cases, elevated levels of antithyroglobulin or antithyroid antibodies in euthyroid participants are positively associated with urticarial flares.[12,13]

Around 15–20% of people have urticaria at least once during their lifetime.[14] Acute urticaria is rather common in young ages, mostly induced by Type I hypersensitivity allergic reactions to food, drug, insect sting, viral infections, or transfusion. Often anaphylaxis due to drugs such as opiates, vancomycin, and radiocontrast media is encountered in clinical practice, which needs to be differentiated from urticaria.

Assessment Tools of Urticaria Disease Activity

In spontaneous urticaria, disease activity is assessed by a robust and simple scoring system named as Urticaria Activity Score (UAS7). UAS7 (Table 3) is a weekly composite sum of the pruritus and number of hives score, for measuring the disease activity.[1] It is a simple questionnaire-based system, which gives the dermatologist a semi-objective evaluation of pruritus and hives experienced by patients [Table 2].[15] The resultant UAS7 score is the sum scores of seven consecutive days (0–42), which determines both the disease activity and efficacy of the ongoing interventions of CSU.

Table 3: Urticaria Activity Score 7 scoring criteria for chronic spontaneous urticaria disease activity

| Score | Wheals | Pruritus |
|-------|--------|---------|
| 0     | None   | None    |
| 1     | Mild (<20 wheals/24 h) | Mild (present with no discomfort) |
| 2     | Moderate (20-50 wheals/24 h) | Moderate (annoying but no impact on daily activity, sleep) |
| 3     | Intense (>50 wheals/24 h) or large confluent areas of wheals | Intense (severe pruritus, interferes daily activities and sleep) |

Sum of score: 0–6 for each day is summarized over 1 week (Minimum 0 maximum 42)

The Angioedema Activity Score (AAS) is also a patient’s self-reported evaluation of the activity of angioedema, which includes scoring of five key factors (duration, physical discomfort, impact on daily activities, impact on appearance, and overall severity) from 0 to 3 of each, respectively (thus a daily score of 0–15).[16] Daily AAS scores can be summed to give 7-day scores (AAS7), 4-week scores (AAS28), and 12-week scores (AAS84), respectively, for treating physician preference.

Diagnosis

The diagnosis should be made by a specific ordered detailed patient history, physical examination, and also some routine laboratory investigations for ruling out any association of systemic autoimmune or autoinflammatory disease.[17] Patient history should include the following:
(a) time of onset of disease; (b) presence of any precipitating factors; (c) association with angioedema; (d) persistence of individual wheal beyond 24 h; (e) use of drugs (nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme [ACE] inhibitors, immunisations, hormones, and alternative remedies); (f) quality of life (QOL); and (g) treatment history, if any [Table 4].

In cases of anaphylaxis, along with urticaria/angioedema signs, other symptoms of organ involvement such as pulmonary tract (wheezing and cough), gastrointestinal (GI) system (vomiting and diarrhoea), nervous system (dizziness), or cardiac system (changes in blood pressure or heart rate) should be evaluated. CSU can also be implicated from infectious status including viral infections (hepatitis B and C, herpes simplex virus),[17] *Helicobacter pylori* infections,[18] and also helminthic parasitic infections.[19]

Other systemic conditions should be ruled out in suspected cases, which include a wide range of disorders including cryoglobulinemia (chronic lymphocytic leukaemia), serum sickness, connective tissue diseases such as systemic lupus erythematosus, thyroid disease, neoplasms (particularly lymphoreticular malignancy and lymphoproliferative disorders), and other endocrine disorders.[20,21] Furthermore, in some cases, careful patient history along with laboratory findings may point toward the requirement of a skin biopsy to rule out dermatomyositis and vasculitis. Although a routine skin biopsy of CU lesions is not recommended, histopathology of urticaria lesion shows predominant lymphocytic infiltrate with polymorphonuclear cells.[22] Urticarial vasculitic lesions typically possess urticarial symptoms lasting >24 h, which is confirmed by a skin biopsy revealing the presence of leukocytoclastic vasculitis.[23] A positive correlation has been found between detectable thyroid autoantibodies and CU though routine assessment for thyroid autoantibodies is not recommended.[12] The CU should also be evaluated through proper patient history and complaints relating to any GI origin, which may apparently link to *H. pylori* infection, coeliac disease, helminthic infections, etc. Although relationship to such problems is weak and inconclusive, it may benefit in select case scenario.

Angioedema is essentially a clinical diagnosis presenting as nonitchy, brawny, nonpitting oedema also with typical undefined margins and without erythema.[16] In angioedema with the absence of coexisting urticaria, evaluation should also be focused for hereditary angioedema, acquired C1 inhibitor deficiency, or ACE inhibitor-associated angioedema. However, a detailed discussion of angioedema without urticaria is beyond the scope of the present article.

**Table 4: Diagnostic tests for urticaria**

| Type                    | Subtype                     | Routine tests                                      | Differential diagnosis tests (for only suspected cases) |
|-------------------------|-----------------------------|----------------------------------------------------|--------------------------------------------------------|
| Spontaneous urticaria   | Acute urticaria             | None                                               | None                                                   |
|                         | CSU                         | CBC, ESR, TSH                                      | Tests for: Infectious disease (e.g., *Helicobacter pylori*); functional autoantibodies; thyroid profile and thyroid antibodies; autologous serum skin test; skin biopsy |
| Inducible urticaria     | Cold urticaria              | CBC, ESR, cold provocation test (with ice cube)    | Tests for cryoproteins rule out especially infections   |
|                         | Pressure urticaria          | CBC, ESR, pressure test (e.g., dermographometer, Fric test) | None                                                   |
|                         | Heat urticaria              | CBC, ESR, heat provocation test                    | None                                                   |
|                         | Solar urticaria             | CBC, ESR, UV and visible light threshold test       | Rule out other light-induced dermatoses                 |
|                         | Symptomatic dermographism   | CBC, ESR                                           | Test with vortex                                        |
|                         | Vibratory angioedema        | Test with vortex                                   | None                                                   |
|                         | Aquagenic urticaria         | Wet cloths at body temperature for 20 min          | None                                                   |
|                         | Cholinergic urticaria       | Exercise and hot bath provocation                  | None                                                   |
|                         | Contact urticaria           | Cutaneous provocation test                         | Skin tests, e.g., prick test                           |

ESR: Erythrocyte sedimentation rate, CBC: Complete blood count, TSH: Thyroid-stimulating hormone, CSU: Chronic spontaneous urticaria, UV: Ultraviolet
Management of Urticaria

General management

The therapeutic approach should be based on elimination or avoidance of the cause or trigger/stimulus, symptomatic pharmacological treatment by reducing mast cell mediator release and/or the effect of these mediators at the target organ, and inducing tolerance. Identifying the cause of urticaria is not possible in most cases; however, good history to rule out causes of inducible urticaria will increase therapeutic efficiency. Avoidance of physical stimuli for the treatment of physical urticaria is suggested but may not always be possible. The aim of therapy for CU is quick and complete symptom control. The authors recommend aiming for complete symptom control in urticaria as safely as possible irrespective of the type of urticaria (CSU/CINDU). Drugs (e.g., nonsteroidal anti-inflammatory drug) causing nonallergic hypersensitivity reactions cannot only elicit but can also aggravate preexisting CSU; elimination of the drug wherever possible is suggested. CSU is often anecdotally reported to be associated with a variety of inflammatory or infectious diseases. These infections include those of the GI tract, such as H. pylori. Even though the association with urticaria is not clear and a meta-analysis shows overall low evidence, H. pylori should be eliminated if the treating physician feels in select cases.

Treatment

First-line therapy

Second-generation non-sedating antihistamines

The mainstay of therapeutic options is directed upon symptomatic relief of urticaria by antagonising the specific actions of H1-receptor-mediated histamine actions upon endothelial cells (the wheal) and on sensory nerves (pruritus). The first-generation antihistamines are reported to have potent anticholinergic effects and sedative actions on central nervous system lasting longer than 12 h, with therapeutic actions only for 4–6 h. Most of them cross blood–brain barrier and interact with brain H1-receptor, leading to disturbed rapid eye movement sleep and cognitive functions. Many drug-drug interactions were also reported for sedating antihistamines. Thus, first-generation antihistamines are no longer the choice in modern urticaria treatment, as currently, there is availability of a wide range of modern low-cost second-generation antihistamines with lesser side effects, without anticholinergic effect (no sedation and cognitive dysfunction) and also with higher efficacy and duration of action, thus better compliance.

Further progress with regard to drug safety was achieved by the development of the newer modern second-generation antihistamines, cetirizine (metabolite of hydroxyzine), loratadine, and fexofenadine, some of which are mostly non-sedating metabolites of earlier sedative antihistamines. More recently, a plethora of second-generation drugs came such as azelastine, desloratadine (the active metabolite of loratadine), ebastine, levocetirizine (the active enantiomer of cetirizine), and rupatadine. Two second-generation drugs, astemizole and terfenadine, were banned for various reports of cardiotoxic effects such as QT prolongation, ventricular arrhythmia, and torsade de pointes and metabolic interaction with ketoconazole or erythromycin. Many out of these second-generation antihistamines do not possess high level of evidence in effectiveness in treating urticaria, and also, considerable clinical differences between them exist. Only seven of them (cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, rupatadine, and bilastine) have been tested in detail in urticaria. Three of the commonly used second-generation antihistamines in India (desloratadine, fexofenadine, and levocetirizine) were extensively evaluated in the management of urticaria for safety and efficacy even up to four-fold elevation of the standard doses. Some reports indicate that according to the receptor occupancy, desloratadine is the most potent (Ki: 0.4 nM), followed by levocetirizine (Ki: 3 nM) and fexofenadine (Ki: 10 nM) (lower the concentration higher is the potency). However, higher occupancy and affinity for H1-receptors should also be evaluated with clinical efficacy and safety. The second-generation drugs’ superior effectiveness is not only attributed to their antihistaminic activities but may also be due to other anti-inflammatory actions such as inhibition of cell adhesion molecules-1, endothelial leukocyte adhesion molecule-1 expression, generation and release of cytokines, and inhibition of eosinophil chemotaxis. In a randomised clinical trial (RCT), it was shown that second-generation antihistamines such as bepotastine, cetirizine, fexofenadine, and olopatadine had similar efficacy in reducing histamine-induced flare when compared to placebo; however, bepotastine has significantly less sedative action when compared to others.

So to sum up, modern second-generation antihistamines should always be considered as the first-line symptomatic treatment for urticaria because of their overall good safety profile, proven efficacy, and broad spectrum of controlling urticarial/angioedema pathological cascades.

Consensus statement 3

Are modern second generation H1-antihistamines to be preferred over first-generation H1-antihistamines in the treatment of urticaria?

There is a strong recommendation to prefer the use of modern second-generation H1-antihistamines over first-generation H1-antihistamines as first line of the treatment of urticaria.
**Second-line therapy**

**Up-dosing of second-generation non-sedating antihistamines**

Numerous clinical studies support the clinical benefit and safety of a higher dosage of antihistamines, even up to fourfold higher than recommended doses of desloratadine, fexofenadine, levocetirizine, etc. So strong recommendation had come from the latest updated GA²LEN/EDF/EAACI/WAO guidelines.[2] It is suggested that the majority of nonresponder urticaria patients will benefit from up-dosing of antihistamines. Thus, up-dosing of modern second-generation antihistamines up to four times of the respective licensed dose should be considered as the second-line treatment for CSU/CINDU.

Studies confirmed the absence of dose-related QT interval prolongation with high doses of fexofenadine as up to 800 mg once daily or 690 mg twice daily for 28 days establishing the safety of the drug in higher doses.[31] Apart from fexofenadine, other drugs with good safety and efficacy data on 4-time elevation standard doses are cetirizine, levocetirizine, and desloratadine.[25] Since levocetirizine is the active enantiomer of cetirizine, the present guideline recommends that only levocetirizine, fexofenadine, and desloratadine should be considered for 4-time elevation, till better safety and efficacy data are available for other molecules.

Before stepping up, we recommend to wait for 1–2 weeks for allowing maximum effectiveness of antihistamines to manifest. Similarly, once under control, a slow step down of antihistamine without losing the beneficial disease control is recommended.

Combining two antihistamines may not afford a simple additive or synergistic result on the antihistamine receptors as they have inverse agonist action on H1-receptors. The efficacy, safety, and drug-drug interaction are not well studied in different antihistamine combinations, but existing evidence suggests that there may not be adequate benefit in combining antihistamines. Rather up-dosing an antihistamine up to fourfold is extensively studied for many antihistamines, and it can be recommended on the virtue of evidence.

Although at standard dosing, there is some evidence that the drug efficiency may differ between molecules as far as receptor-binding capacity and clinical efficiency in wheal control are concerned, there are not much evidence if the drugs differ in efficacy and safety parameters when up dosed. Hence, the present guidelines suggest against combining antihistamines or shifting between different antihistamines if the second line of treatment fails to give adequate disease control and recommend going to the third line of treatment instead.

**Consensus statement 4**

Is an increase in the dose to fourfold of modern second-generation H1-antihistamines useful as second-line treatment and to be preferred over other treatments in urticaria?

There is a strong recommendation of a trial of up to four-fold dose of modern second-generation H1-antihistamines as second line in the algorithm of treatment of urticaria.

**Corticosteroids**

Although oral corticosteroids are frequently used in CSU patients who are resistant to antihistamine therapy, controlled studies are lacking [Table 5]. A retrospective analysis among 750 patients reports that 50% of patients with antihistamine-resistant CU were successfully treated with a single course of prednisone (25 mg/day for 3 days, tapered to 12.5 mg/day for 3 days, and then, 6.25 mg/day for 4 days).[32] In a case study among 10 Indian CSU patients, 2 months of methylprednisolone 16 mg BD along with levocetirizine 5 mg daily caused a significant reduction in mean UASs.[33] However, in view of the severe adverse effects associated with long-term corticosteroid therapy, systemic steroids are recommended to be used sparingly only for a short period for managing acute exacerbations when all other therapies have failed or there is an emergency.[57] Proper guidelines for dose and duration of oral corticosteroids in CU management are also lacking.

**Cyclosporine**

Low-dose cyclosporine is often considered in severe unremitting cases of CSU/CINDU. Although T-cell-mediated action of cyclosporine is widely accepted in immunosuppression, inhibition of basophil activity and mast cell degranulation is also known.[32,58] In a double-blind RCT, cyclosporine at doses of 3–5 mg/kg/day for 16 weeks along with daily cetirizine was reported to significantly ameliorate symptoms of CSU patients.[34] Similarly, another RCT reported that cyclosporine (4 mg/kg/day) in 30 autologous serum skin test (ASST)-positive patients for 4-week therapy, significantly reduced UAS scores. However, there was a relapse after 6 weeks of drug holiday.[35] A study among ASST-positive Indian patients with cyclosporine at a dose of 3 mg/kg/day for 12 weeks also reveals substantial improvement in UAS scores within 2 weeks of therapy. There was complete remission in three out of four CSU patients in the study.[36] Efficacy of low-dose cyclosporine (1.5–2.5 mg/kg/day) over 5 months was found promising among 30 ASST-positive autoimmune urticaria patients.[37] After 1-year follow-up, 20 out of 23 patients were under complete remission and three relapsed.[37] Another study that compares cyclosporine (4 mg/kg/day)
### Table 5: Comparison among pharmacotherapies in refractory chronic urticaria patients who are resistant to high dose or combination antihistamine therapy

| Drug                          | Dose                        | Onset of improvement | Evidence | Comments | Monitoring |
|------------------------------|-----------------------------|----------------------|----------|----------|------------|
| Corticosteroids (short course) | 0.3–0.5 mg/kg for maximum 7–10 days | 1–5 days | Low (2 case series)<sup>[32,33]</sup> | Early remission during exacerbations; potent adverse effects on long-term usage | Not applicable for long-term use. Recommended only for short courses. Every 2–4 weeks urea, creatinine, lipids, glucose, BP. |
| Cyclosporine                 | 3–5 mg/kg/day               | 5–7 days             | High: 2 good quality RCTs,<sup>[34,35]</sup> several case series<sup>[36–40]</sup> | Good efficacy in pediatric, in steroid-dependent patients; moderately expensive; risk of nephrotoxicity and other side effects | Every 2–4 weeks urea, creatinine, lipids, glucose, BP. |
| Omalizumab                   | 150–300 mg every 4 weeks   | 1–2 weeks            | High (many RCTs)<sup>[41–44]</sup> Many case series<sup>[45–51]</sup> | Expensive; risks of anaphylaxis | Nil |
| H2-blockers                  | Standard dosage as used in practice | NA (as combined with H1 antihistamines) | Low (2 case studies)<sup>[45,48–51]</sup> | Cheap, lacking proper evidences; H1 + H2 combination as add-on therapy | Nil |
| Methotrexate                 | 7.5–15 mg/week              | 3 weeks to months   | Low (1 RCT<sup>[52]</sup>, 2 case reports<sup>[53–56]</sup>) | Effective for steroid-dependent CSU; cheap; hepatotoxicity, blood dyscrasias, GI adverse effects | CBC, platelets, LFT |
| Autologous serum therapy     | 0.05 ml/kg/week             | 4–7 weeks            | Low (2 RCT, 2 case series) | Cheap, effective in autoimmune urticaria, mixed results of efficacy; no adverse effects | Nil |
| Montelukast                  | 10 mg daily                 | 2–4 weeks            | Medium (4 RCTs with contradictory findings) | Cheap, mixed results, effective in combination with antihistamine, effective in food and aspirin-induced cases; good safety | Nil |
| Dapsone                      | 50–100 mg daily             | 1–6 weeks            | Low (2 RCTs) | Cheap, effective in urticarial vasculitis; risks of methaemoglobinaemia, hepatotoxicity, contraindicated in G6PD deficiency | G6PD, LFT, CBC |
| Doxepin                      | 10 mg thrice daily          | 2–3 weeks            | Low (2 RCTs) | Beneficial in associated severe pruritus, depression; causes dry mouth, drowsiness | BP |
| Hydroxychloroquine           | 200 mg daily                | 10–12 weeks          | Low (1 RCT) | Relatively safe; but risks of retinopathy on long-term use | Ophthalmologic evaluation yearly |
| Sulfasalazine                | 500–2000 mg daily           | 3–6 months           | Very low (case studies) | Cheap, pressure urticaria and angioedema; side effects of leukopenia, nausea, headache | CBC, LFT, RFT |
| Mycophenolate                | 1000 mg once or twice daily | 12–14 weeks          | Low (2 case series) | Costly; high risk of infection | CBC, LFT, RFT |

CBC: Complete blood count, LFT: Liver function tests, RFT: Renal function tests, RCTs: Randomised controlled trials, G6PD: Glucose-6-phosphate dehydrogenase, BP: Blood pressure, NA: Not available, GI: Gastrointestinal, CSU: Chronic spontaneous urticaria
for 1-month versus 3-month therapy suggested that the results are equivalent in terms of clinical benefit. There was no significant difference in frequency of responses, reduction of UAS in either group.\textsuperscript{[38]} Another RCT among 120 CU participants with cyclosporine (3 mg/kg) showed that 62% of the patients benefited in 3 months, 20% benefited after long-term therapy, but 18% did not get any response.\textsuperscript{[39]} Cyclosporine therapy is also beneficial in elevated IgE levels associated CU, reported in a case series of over 21 patients.\textsuperscript{[40]} However, potential renal impairment effects of cyclosporine (which may be reversible on stopping) and hypertension are often encountered; thus, continuous blood pressure and blood urea and creatinine monitoring are required during the course of therapy.

**Omalizumab**

The US Food and Drug Administration and the European Medicines Agency have approved omalizumab for both adults and adolescents with refractory CSU. A growing number of study reports its benefit in standard therapy failure cases of urticaria and angioedema.\textsuperscript{[41-44,58-65]}

Omalizumab is a humanised monoclonal IgG antibody against IgE, with low immunogenicity. Omalizumab consists of 95% IgG1 kappa human framework and 5% mouse sequence, which is hidden from the immune system when omalizumab binds to IgE.\textsuperscript{[45]} It inhibits binding of IgE to FceRI on the surface of mast cells and basophils. Omalizumab binds to the Ce3 domain of IgE, forming trimers or hexamers and preventing it from binding to FceRI on the surface of mast cells and basophils. However, omalizumab cannot bind to receptor-bound IgE.\textsuperscript{[46]} Omalizumab binds to IgE and reduces free IgE levels, leading to downregulation of FceRI on mast cells and basophils.

Results from proof-of-concept X-CUISITE study supported the efficacy and safety of omalizumab.\textsuperscript{[47]} Another Phase II study MYSTIQUE on omalizumab showed improvement in symptoms of CSU with 300 mg omalizumab, with no additional benefit for 600 mg omalizumab. Three Phase III studies were conducted ASTERIA I, ASTERIA II, and GLACIAL.\textsuperscript{[42-44]} The studies established up to 71% of itch reduction in CSU with omalizumab after 12 weeks. Rapid itch reduction was seen with the first dose of 300 mg. Up to 44% achieved zero UAS 7 score with omalizumab at 12 weeks. About 78% Dermatology Life Quality Index (DLQI) reduction is seen from baseline at week 12. Overall safety profile was found to be good except for minor increase in upper respiratory tract infection, headache, and arthralgia.\textsuperscript{[49]}

Numerous reports exist about its efficacy in cholinergic urticaria,\textsuperscript{[47]} cold urticaria,\textsuperscript{[60]} solar urticaria,\textsuperscript{[61]} heat urticaria,\textsuperscript{[62]} symptomatic dermographism,\textsuperscript{[63]} and delayed pressure urticaria.\textsuperscript{[64]} A double-blind RCT over 323 refractory urticaria patients with moderate-to-severe CSU demonstrated a high outcome with omalizumab (150 mg or 300 mg subcutaneous [SC] injection) at every 4 weeks apart for 12 weeks.\textsuperscript{[45]} Safety data were also reported to be encouraging at that study. Although regarding safety data, it has been infrequently associated with anaphylaxis due to its immunological origin. Omalizumab efficacy is also validated in Indian population with CU not responding to other therapies.\textsuperscript{[43]} Several more case series and reports conform omalizumab superiority in the treatment of refractory cases of CSU/CINDU.\textsuperscript{[46-51]}

However, in Indian context, the cost of treatment and the requirement for SC administration in a clinician’s office may limit its use.

**First-generation Antihistamines**

The consensus believes that though modern second-generation antihistamines should be preferred in the treatment, in select cases, hydroxyzine may be used in refractory cases, because of easy availability, cheaper costs, and long experience of the Indian doctors using the molecule.

**H2-Blockers**

A systematic Cochrane review concluded that combinations of H1- and H2-antihistamines in a smaller number of CU patients reported better outcome than H1-antihistamines alone but also pointed out the weak level of evidence.\textsuperscript{[52]} An RCT among 45 CU patients also reported that adding ranitidine with terfenadine gave superior results to terfenadine alone in terms of itch, but effect on wheal or swellings was insignificant.\textsuperscript{[45]} Most RCTs and other case studies show conflicting and disappointing results about benefit of adding H2-antihistamines.\textsuperscript{[54,55]} The present guidelines recommend against random or routine use of H2-antihistamine.

**Methotrexate**

Some case studies and series are in support of methotrexate in relieving symptoms for corticosteroid-dependent CSU.\textsuperscript{[53,56,66]} and also urticarial vasculitis.\textsuperscript{[57]} An Indian
RCT of small sample size concluded that adding methotrexate (15 mg weekly) for 3 months in refractory CU cases did not show any significant additional benefit over H1-antihistamines.\[^{[66]}\] Though very limited data are available, the authors suggest that methotrexate may be considered as an alternative in selected cases of refractory urticaria especially in Indian perspective, for its low cost, easy availability, easy dosing schedule and wide acceptance.

### Autologous Serum Therapy

A placebo-controlled trial over 56 CU patients suggested that ASST-positive CU could benefit from 8 weeks of aspartate transaminase (AST) but not in other CU subforms.\[^{[69]}\] An Indian multicentre, prospective study also analysed that weekly AST injections for 9 weeks showed significant improvements in both ASST-positive and ASST-negative patients with a sustained action for 4-month follow-up period after the last dose.\[^{[70]}\] Another RCT comparing AST and autologous whole blood injections in 88 CU patients found no statistically significant difference in terms of efficacy and QOL improvement.\[^{[71]}\] Case series reported from India showed that AST is of only moderate efficacy in small number of the treated patients.\[^{[72]}\] A recent RCT shows disappointing results of AST therapy as compared to saline injections as control group.\[^{[73]}\] The present consensus suggests that AST may be tried in refractory urticaria for its low cost and good safety profile, but evidence for potential benefit is low.

### Montelukast

Leukotriene antagonist montelukast at 10 mg/day was reportedly effective for the treatment of CU, both as monotherapy or in combination with H1-antihistamines although the treatment effect observed was small.\[^{[74-80]}\] Numerous results of clinical studies have been inconsistent, some demonstrating a superior response\[^{[79,80]}\] and others showing an inferior response with montelukast when compared to antihistamines.\[^{[74]}\] Montelukast monotherapy has been especially found beneficial in food additives and NSAID-induced urticarial symptoms.\[^{[79,80]}\] The present guidelines suggest that there is no added advantage of montelukast over standard antihistamines and therefore should not be considered as therapeutic option in regular basis and should only be reserved as an adjuvant in select refractory cases.

### Dapsone

A small double-blind placebo controlled study on 22 patients clearly reflects about substantial efficacy of dapsone at dose of 100 mg/day for 6 weeks in CSU patients for controlling hives and itch.\[^{[81]}\] Another RCT clearly shows that the combination of dapsone with antihistamine versus antihistamine alone caused a persistent decrease in UAS scores also with complete remission in some cases.\[^{[82]}\] Moreover, some case studies also exist with reports of its prominent efficacy upon urticarial vasculitis\[^{[83,84]}\] and idiopathic angioedema.\[^{[85]}\] Dapsone is known to confer with side effects such as methaemoglobinemia, peripheral neuropathy, hepatotoxicity. Ruling out G6PD deficiency is mandatory before initiation of dapsone. Due to the lack of evidence and possibility of serious side effects, the consensus guidelines recommend against the use of dapsone in the treatment of CSU/CINDU.

### Doxepin

Doxepin is primarily a tricyclic antidepressant but possesses H1/H2-antagonistic action. In a double-blind cross-over study, doxepin (10 mg TDS) was found to be more efficacious with lesser sedation than diphenhydramine (25 mg TDS) in CU patients.\[^{[86]}\] Another RCT results also support doxepin (10 mg TDS) compared to pheniramine (22.5 mg TDS) in terms of improvement and sedation.\[^{[87]}\] Although there is a paucity of evidence, limited available RCT experience of the consensus group suggests that doxepin can be used as a third line of treatment in select cases of CSU/CINDU, especially when cyclosporine and omalizumab are unavailable, inaccessible, or contraindicated.

### Hydroxychloroquine

Only one double-blind RCT exists, demonstrating that 18 CU patients for an intervention of hydroxychloroquine (200 mg/day) for 12 weeks lead to improvement in QOL scores. ASST reactivity had no correlation with its responsiveness.\[^{[88]}\] The consensus guideline recommends against the use of hydroxychloroquine in urticaria.

### Mycophenolate

In a small trial without control, mycophenolate mofetil (MMF) in doses of 1000 mg BD for 12 weeks was found to decrease UAS in refractory CU patients along with steroid-free disease activity control.\[^{[89]}\] A retrospective analysis of 19 patients with autoimmune and chronic idiopathic urticaria, 89% got control over urticaria symptoms within 14 weeks of MMF (1000 mg to 6000 mg daily in two divided doses) but frequently reported GI adverse effects.\[^{[90]}\] Moreover, case study depicts MMF to be successful in treating urticarial dermatitis\[^{[91]}\] and cyclosporine intolerant CU patients.\[^{[92]}\] However, because of low evidence, doubtful effect, high cost, and incidence of adverse effects present guideline suggests against using of MMF in CSU/CINDU.

### Miscellaneous Treatments

Tumour necrosis factor-alpha antagonists in cases of delayed pressure urticaria and intravenous immunoglobulin in cases of refractory CSU were used successfully in odd case reports. UV-A1, PUVA, and narrowband UV-B were used as adjuvant with antihistamines for refractory urticaria.\[^{[93]}\]
Non-sedative (second-generation) antihistamine

If nonresponsive in 1 week

Up to four-fold elevation of the non-sedative (second-generation) antihistamine

Very short course (5–7 days) of corticosteroid may be added if there is acute life-threatening presentation including severe associated angioedema

Strong Evidence: Cyclosporine Omalizumab

Weak Evidence**: First-generation antihistamine (Hydroxyzine) $ Methotrexate Autologous Serum therapy Doxepin

Figure 1: ALGORITHM of management of urticaria. *: Safety evidence of up-dosing is available for levocetirizine, desloratadine and fexofenadine, ++: May be considered in selected situation, $: Should be considered for not more than 2 months as limited data are available for long-term safety

Consensus statement 6

Should hydroxyzine, autologous serum therapy, doxepin and methotrexate be used in the treatment of urticaria.

There is a suggestion to use hydroxyzine, autologous serum therapy, doxepin, and methotrexate in select cases of refractory urticaria especially when cyclosporine and omalizumab are unavailable, inaccessible, or contraindicated.

Recommendation: [Figure 1]

- Our recommendation is to start with a second-generation antihistamine and assess the benefit for at least 7 days using the UAS7 criteria
- If effectiveness is not achieved by conventional dosage, then subsequently increase the dose up to 4 times the recommended one, but only in case of levocetirizine, fexofenadine, and desloratadine among the drugs currently available in India, the safety data are established with a high level of evidence
- A short course (not more than 5–7 days) of corticosteroids with a dose of 0.5 mg/kg/day of prednisolone equivalent may be given for decreasing the acute underline inflammation, mostly encountered with associated angioedema, breathing discomfort, wheezing, allergic rhinitis, etc. We strongly recommend against the long-term use of corticosteroids due to its potential adverse effect
- In patients whom even up to 4 times of up-dosing of second-generation antihistaminic do not control the symptoms, either omalizumab or cyclosporine can be considered. Majority of cases, antihistamine-refractory CSU patients, respond to omalizumab (anti-IgE) as per high-quality evidence of randomised controlled trials. Hence, omalizumab, a humanised monoclonal antibody against IgE, can be considered in select cases of CSU as the third line of treatment. However, due to its high cost, in Indian socioeconomic conditions, cost-to-benefit ratio is the major concern for practitioners as also for patients. Hence, we also recommend cyclosporine, which also has validated efficacy in refractory urticaria, to be also considered as the third line of therapy, for Indian scenario. However, due to a high incidence of adverse effects such as hypertension, nephrotoxicity, gingival hyperplasia, hypertrichosis, and altered lipid profile, the use of cyclosporine should be strictly monitored as per standard guidelines. Most reported cyclosporine doses in clinical trials to be effective were 4-5 mg/kg.[34-36] Although low-dose (2–3 mg/kg) therapy had also been shown to be effective in some reports.[37] We suggest against the continuous use of cyclosporine for more than 3–4 months and also to stick to the monitoring guidelines strictly
- The last options of pharmacological interventions are with molecules with low level of evidence, a first-generation antihistamine hydroxyzine, methotrexate, AST, and doxepin. Weekly once dosing of methotrexate at 10–15 mg may be cost-effective, have a steroid-sparing effect, as based on limited clinical data. AST has conflicting evidence and may be tried in some select scenario as the cost burden is very low to the patient. Although first-generation antihistamines are going out of favour globally due to high incidence of sedation and other side effects, the authors believe that first-generation antihistamine, especially hydroxyzine, still has place in the treatment of CSU, in select cases in Indian scenario.

In children

The use of first-generation sedative antihistamines in infants and children is strongly discouraged by most consensus reviews. Cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine have been well studied in children, and their long-term safety has been well established in the paediatric population. Hence, these drugs with proven efficacy and established long-term safety in paediatric population are recommended. Furthermore, further selection is also dependent upon available formulations, which are suitable for children.

Key concepts of urticaria management in children are:
1. Elimination of underlying causes and/or eliciting triggers wherever possible
2. Second-generation H1-antihistamines are the mainstay of treatment aimed at providing symptom relief. The safety of up-dosing has not been validated in children. First-generation H1-antihistamines should be avoided
3. Difficult cases may require other therapeutic interventions, the risk-benefit ratio being carefully analysed, as there is a paucity of supporting evidence.

4. Corticosteroids should be avoided and if used, should strictly be limited for short periods only (3–7 days).[94]

**In pregnancy and lactation**

It is best to avoid all antihistamines in pregnancy, especially during the first trimester, although, till now, there is no reports of teratogenicity and birth defects in pregnant women using modern second-generation antihistamines. However, only small sample size studies are available for cetirizine and one large meta-analysis for loratadine. Loratadine and cetirizine are classified as the US Food and Drug Administration Pregnancy Category B drugs, implying that there is no evidence of harm to the foetus during pregnancy, although well-controlled studies in humans are not available to exclude harmful effects. Clinicians, because of its long safety record often choose chlorphenamine. Hydroxyzine is one antihistamine, which is mentioned to be contraindicated during the early stages of pregnancy in some manufacturers’ insert.[95,96] All H1-antihistamines are excreted in breast milk in low concentrations. The use of second-generation H1-antihistamines is advised as nursing infants may have sedation and impaired cognitive development from the old first-generation H1-antihistamines transmitted in breast milk. Cyclosporine is not teratogenic, but it is embryotoxic in animal models and is associated with preterm delivery and low birth weight in human infants. Hence, the use of cyclosporine should be judged carefully in CSU calculating the risk-benefit ratio. Long-term safety of omalizumab is not established in pregnancy and lactation.

**In hepatic impairment**

Mizolastine is contraindicated by significant hepatic impairment. Chlorphenamine and hydroxyzine should also be avoided in severe liver disease because their sedating effect is inappropriate. Other second-generation antihistamine may be used with caution weighing the risk benefit ratio.

**Renal impairment**

The dose of cetirizine, levocetirizine, and hydroxyzine should be halved in patients with impaired renal failure. Cetirizine and levocetirizine should not be used in severe renal impairment. Loratadine and desloratadine should be used with caution in severe renal impairment.

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**Conflicts of interest**

There are no conflicts of interest.

**What is new?**

This guideline provides a comprehensive and evidence based analysis of evaluation and management of urticaria with an Indian perspective.

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