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CHAPTER

4

# Management



## Acute Urticaria

### Acute Urticaria: Differentiation from Anaphylaxis

- Acute urticaria and angioedema should be differentiated from anaphylaxis.
- In anaphylaxis, urticaria/angioedema is associated with signs and symptoms in organs other than the skin:
  - The pulmonary tract (wheezing and cough)
  - Gastrointestinal system (vomiting and diarrhea)
  - Nervous system (dizziness and loss of consciousness)
  - Cardiac system (changes in blood pressure or heart rate)

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- Epinephrine should be prescribed if the diagnosis of anaphylaxis has not been excluded.

***Acute urticaria and anaphylaxis***
Anaphylaxis should always be excluded from acute urticaria. This is of utmost important from prognostic and management point of view.

### Treatment of Acute Urticaria

- Antihistamines are effective in most cases and recommended as first-line therapy.
- First-generation antihistamines are rapidly acting but they can produce sedation and impaired motor skills as they can cross the blood–brain barrier. Adult patients and parents of child patients should be made aware of the potential side effect.
- These impairments are less evident or not evident with second-generation antihistamines.
- A brief course of oral corticosteroids may be prescribed in antihistamines refractory patients.

## Chronic Urticaria

### Monitoring

- In management of chronic urticaria score. The UAS7 to be determined to assess disease activity and response to treatment.

### Quality of Life

- To assess the impact of disease on QoL in clinical practice.

### Determining the Threshold/Nature of Eliciting Factors

- The threshold of the eliciting factor(s) to be determined to assess severity, for example, critical temperature and stimulation time thresholds for cold provocation in cold urticaria.
- The severity of symptoms and the nature and amount of the stimulus vary from one patient to another. For example, a patient with grass pollen or peanut allergy is asymptomatic when not in contact with the stimulus, and a cold urticaria patient can be asymptomatic in a warm climate. Management should take these variations into consideration.

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## Basic Approach

- The classification of different subtypes is to be done for proper diagnosis.
- Therapeutic approach is universal and based on the same principles as in other mast cell-dependent diseases in the field of allergy:
  - Elimination/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
  - Inducing tolerance.

***Principles in approach***

1. Elimination/avoidance of triggers
2. Symptomatic pharmacological treatment
3. Inducing tolerance

## Avoidance of Triggers

1. Drugs
2. Physical stimuli
3. Infectious agents and inflammatory processes

### *Drugs*

- Whenever suspected the culprit drugs should be omitted entirely or substituted by another class of agents.
- Drugs causing nonallergic hypersensitivity reactions (example NSAID) can trigger as well as aggravate pre-existing chronic spontaneous urticaria (CSU).
- Angiotensin converting enzyme (ACE) inhibitors to be stopped in patients of angioedema without wheals.

### *Physical Stimuli*

- Avoidance of physical stimuli for the treatment of physical urticaria is to be attempted but not always practically possible.
- The patient should have adequate knowledge about the physical properties of the respective stimulus to recognize and control exposure in their normal daily life.
- In delayed pressure urticaria/angioedema and in symptomatic dermographism, pressure is defined as force per area.

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(Simple measures, such as broadening of the handle of heavy bags for pressure urticaria or reducing friction in case of symptomatic dermographism may be helpful.)

### *Infectious Agents and Inflammatory Processes*

- CSU is often associated with a variety of inflammatory or infectious diseases.
- These infections should be treated appropriately, include those of the gastrointestinal tract, such as *H. pylori*, bacterial infections of the nasopharynx, bowel parasites, intestinal candidiasis, etc.
- In chronic inflammatory processes due to various other diseases like gastritis, reflux esophagitis, or inflammation of the bile duct or gallbladder have been identified as potentially causative for CSU.
- The frequency and relevance of infectious diseases varies between different patient groups and different geographical regions.

## Approach in a Case of Urticaria

- Regional differences in causative factors occur in urticaria due to different traditional diets and different prevalence of infections. So it is not necessary to explore all possible causative factors in all patients.
- First step in diagnosis is a thorough history, as described in the Chapter 1 (Diagnosis).
- The second step of the diagnosis is the physical examination of the patient. This should include a diagnostic provocation test including drug, food, and physical tests where it is indicated by history.

## Algorithmic Approach

- An algorithm needed (step up or step down) in management of chronic urticaria
- Acute urticaria usually self-limited. Treatment focuses on symptomatic relief
- Complete symptom control in urticaria as safely as possible to be attempted

- For urticaria treatment, as in other allergic or immunologic diseases, an algorithm is needed to both serve the majority of

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patients with easy-to-treat symptoms and those being more refractory to treatment.
- The need for treatment within this algorithm may vary over time (step up or step down).
- Acute urticaria differs from all other types as it is self-limited. Treatment is usually focused on symptomatic relief.
- Complete symptom control in urticaria as safely as possible is to be attempted (strong recommendation/clinical consensus following the WHO constitution in conformity with the charter of the United Nations).

## Reduction of Functional Autoantibodies

- Little experience in the treatment for CSU by direct reduction of functional autoantibodies by plasmapheresis.
- Plasmapheresis is of temporary benefit in individual, severely affected patients.
- Due to high costs, this therapy is suggested for autoantibody-positive CSU patients who are unresponsive to all other forms of treatment.

## Role of Total IgE Estimation and Basophil Histamine Release Assay

- A higher total IgE indicates a higher probability of responsiveness to omalizumab, whereby a normal level indicates higher responsiveness to cyclosporine.
- On the contrary a positive basophil histamine release assay (BHRA) indicates higher cyclosporine responsiveness, while negative BHRA indicates higher omalizumab responsiveness

## Dietary Management

- IgE-mediated food allergy rarely cause of CSU
- Pseudoallergic reactions to naturally occurring food ingredients and to food additives seen
- Type I-allergens avoidance clears urticaria usually within 24–48 hours, in pseudoallergy, it may take minimum of 3 weeks.

- IgE-mediated food allergy is rarely the underlying cause of CSU. If identified, the specific food allergens need to be omitted as far as possible.

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- In a subgroup of CSU patients, pseudoallergic reactions (non-IgE-mediated hypersensitivity reactions) to naturally occurring food ingredients and in some cases to food additives have been seen. Similar to drugs, pseudoallergens can both elicit and aggravate CSU.
- Avoidance of type I allergens clears urticaria symptoms within 24–48 hours if the relevant allergens are eliminated rapidly, whereas in pseudoallergy, a diet must often be maintained for a minimum of 3 weeks before beneficial effects are observed.
- Success rates may vary considerably due to regional differences in food and dietary habits. More research is necessary on the effect of foodstuffs in causing urticaria, particularly in areas where the daily diet is greatly different from the one in Western Europe.

## Role of Specific IgE/Skin Prick Test

Patients with a known sensitization based on specific IgE to food should only avoid these food items if there is relevant information, e.g., double blind oral provocation test or a clear history, to prove that the sensitization has a clinical relevance for urticaria (strong recommendation/high level of evidence).

## Role of Pseudoallergen-free Diets

The use of pseudoallergen (nonallergic–hypersensitivity reaction agents) free diets in the extended diagnostic program of chronic spontaneous urticaria has been recommended in patients with daily or almost daily symptoms only (strong recommendation/high-quality evidence).

## Inducing Tolerance

Inducing tolerance can be useful in some subtypes of urticaria. Examples are cold urticaria, cholinergic urticaria, and solar urticaria, where even a UV-A therapy has been proven to be effective within 3 days. However, tolerance induction is only lasting for a few days; thus, a consistent daily exposure to the stimulus just at threshold level is required which, for example, in case of cold baths is often not accepted by patients.

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## Symptomatic Pharmacological Treatment

***Symptomatic control by antihistamines***

- The main aim of treatment is the symptomatic relief
- Continuous treatment with H1-antihistamines is definitely required
- Some cases may be refractory to H1-antihistamines.

- The main option in therapies aim at symptomatic relief is to reduce the effect of mast cell mediators such as histamine, PAF, and others on the target organs. Many symptoms of urticaria are mediated primarily by the actions of histamine on H1-receptors located on endothelial cells (the wheal) and on sensory nerves (neurogenic flare and pruritus).
- Topical antipruritic agents such as menthol containing emollient can be of symptomatic relief.
- Continuous treatment with H1-antihistamines is of utmost importance in the treatment for urticaria as:
  - Most of symptoms are originated by histamines action
  - Mechanism of action of antihistamines are inverse agonists with preferential affinity for the inactive state of the histamine H1-receptor and stabilize it in this conformation, shifting the equilibrium toward the inactive state
  - Clinical data also support this
  - Safety data are available for use of several years continuously.
- In some cases, especially of CSU, other mast cell mediators (PAF, leukotrienes, cytokines) are also involved and a pronounced cellular infiltrate including basophils, lymphocytes, and eosinophils may be observed. These may respond completely to a brief burst of corticosteroid and may be relatively refractory to antihistamines.

## Advantages of Treatment by Second Generation of Antihistamines

***Modern second-generation H1-antihistamines versus first-generation H1-antihistamines in treatment of urticaria:***

Modern second-generation H1-antihistamines are to be preferred over first-generation H1-antihistamines in the treatment of urticaria (strong recommendation/high level of evidence).

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- The older first-generation antihistamines have prominent anticholinergic effects and sedative actions on the central nervous system (CNS), which last longer than 12 hours, whereas the antipruritic effects last only for 4–6 hours.
- These sedating antihistamines have many interactions with alcohol and drugs affecting the CNS, such as analgesics, hypnotics, sedatives, and mood-elevating drugs.
- First-generation antihistamines can interfere with rapid eye movement sleep and impact on learning and performance.
- The side effects of first-generation H1-antihistamines are most pronounced in promethazine, diphenhydramine, ketotifen, and chlorpheniramine. They penetrate the blood–brain barrier, bind to H1-receptors in the CNS, and interfere with the neurotransmitter effects of histamine. Impairment is particularly prominent during multitasking and performance of complex sensorimotor tasks such as driving.
- Old first-generation H1-antihistamines are a particular concern in the elderly in whom they increase the risk of impaired cognition, inattention, disorganized speech, altered consciousness, and falls. The doses of drugs such as diphenhydramine, hydroxyzine, and doxepin, used in urticaria, are massive compared with the doses actually proven to be effective for the treatment of insomnia (i.e., to produce sedation), for example doxepin 3 mg.
- Modern second-generation antihistamines are minimally or not sedating and free of anticholinergic effect. 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 nonsedating metabolites of earlier sedative antihistamines. More recently, acrivastine, azelastine, bepotastine, bilastine, desloratadine, the active metabolite of loratadine, ebastine, epinastine, levocetirizine, the active enantiomer of cetirizine, mequitazine, mizolastine, olopatadine, and rupatadine have been added to the list of modern second-generation antihistamines.
- Many of these antihistamines have not been appropriately studied in urticaria, and there are considerable clinical differences between them.

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- Modern second-generation antihistamines should be considered as the first-line symptomatic treatment for urticaria because of their good safety profile. However, up to date, well-designed clinical trials comparing the efficacy and safety of modern second-generation H1-antihistamines in CSU are largely lacking.

## Up-dosing of Antihistamines

***Up-dosing of second-generation antihistamines:***
A trial of up to fourfold dose of modern second-generation H1-antihistamines as second-line has been recommended in the algorithm of treatment.

- Numerous studies showed the benefit of a higher dosage of antihistamines in individual patients using up to four-fold higher than recommended doses of bilastine, cetirizine, desloratadine, levocetirizine, fexofenadine, rupatadine desloratadine, and levocetirizine.
- Majority of patients with urticaria not responding to single dose will profit from up-dosing of antihistamines.
- Modern second-generation antihistamines at licensed doses are first-line treatment in urticaria, and up-dosing is second-line treatment.

***Second-generation H1-antihistamines be taken regularly or as needed?***
Modern second-generation oral H1-antihistamines to be taken continuously in the lowest necessary dose rather than on demand (strong recommendation/high-quality evidence).

***Different H1-antihistamines be used at the same time?***
Preferably up-dosing modern second-generation oral H1-antihistamines that do not cause sedation up to four-fold (strong recommendation/high-quality evidence) instead of combining different H1-antihistamines at the same time (strong recommendation/low-quality evidence) has been advocated.

## Algorithmic Approach

Recommended treatment algorithm for urticaria [(The EAACI/gA92) LEN/EDF/WAO guideline 2022].

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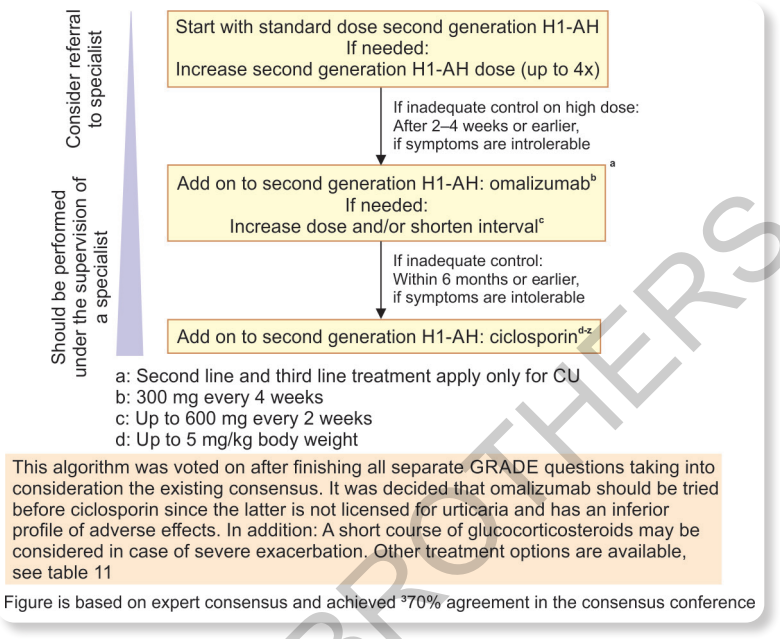


Recommended treatment algorithm for urticaria (Joint Task Force on Practice Parameters by American Academy of Allergy, Asthma and Immunology [AAAAI], American College of Allergy, Asthma and Immunology [ACAAI] and Joint Council of Allergy, Asthma and Immunology 2014)

***Recommended step care approach by American guideline***

Treatment with hydroxyzine or doxepin can be considered in patients whose symptoms remain poorly controlled with dose advancement of second-generation antihistamines and/or addition of one of more of the following: H2 antihistamines, first generation H1 antihistamines at bedtime, and/or antileukotrienes (step 3).

***Step 1:***

- Monotherapy with second-generation antihistamines
- Avoidance of triggers (e.g., NSAIDs) and relevant physical factors if physical urticaria/angioedema syndrome is present.
- Begin treatment at step appropriate for patient's level of severity and previous treatment history.
- At each level of step-approach, medication(s) should be assessed for patient tolerance and efficacy.
- Step-down in treatment is appropriate at any step, once consistent control of urticaria/angioedema is achieved.

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***Step 2:***

One or more of the following:

- Dose advancement of second-generation antihistamines used in Step 1:
- Add another second-generation antihistamine.
- Add H2-antagonist.
- Add leukotriene receptor antagonist.
- Add first-generation antihistamine to be taken at bed time.

***Step 3:***

- Dose advancement of potent antihistamine (e.g., hydroxyzine or doxepin) as tolerated

***Step 4:***

- Add an alternative agent
- Omalizumab or cyclosporine
- Other anti-inflammatory agents, immunosuppressants, or biologics

British Association of Dermatologists guidelines for the management of people with chronic urticaria 2021 **(Flowchart 4.1)**.

## Therapeutic Possibilities for Antihistamines Refractory Patients

- Antihistamines in high dose will control symptoms in the majority of patients with urticaria in general practice.
- Consider switching from one second-generation H1 antihistamine to another in unresponsive patients
- A first-generation antihistamine may be added at night along with second generation at morning.
- Alternative treatments are needed for the remaining unresponsive patients.
- Before changing to an alternative therapy, it is recommended to wait for 1–4 weeks to allow full effectiveness.
- Consider addition of montelukast in addition to second-generation H1 antihistamine in unresponsive patients
- As the severity of urticaria may fluctuate, and as spontaneous remission may occur at any time, it is also recommended to re-evaluate the necessity for continued or alternative drug treatment every 3–6 months.
- Except for omalizumab and cyclosporin A, which both have restrictions due to their high cost, many of the alternative

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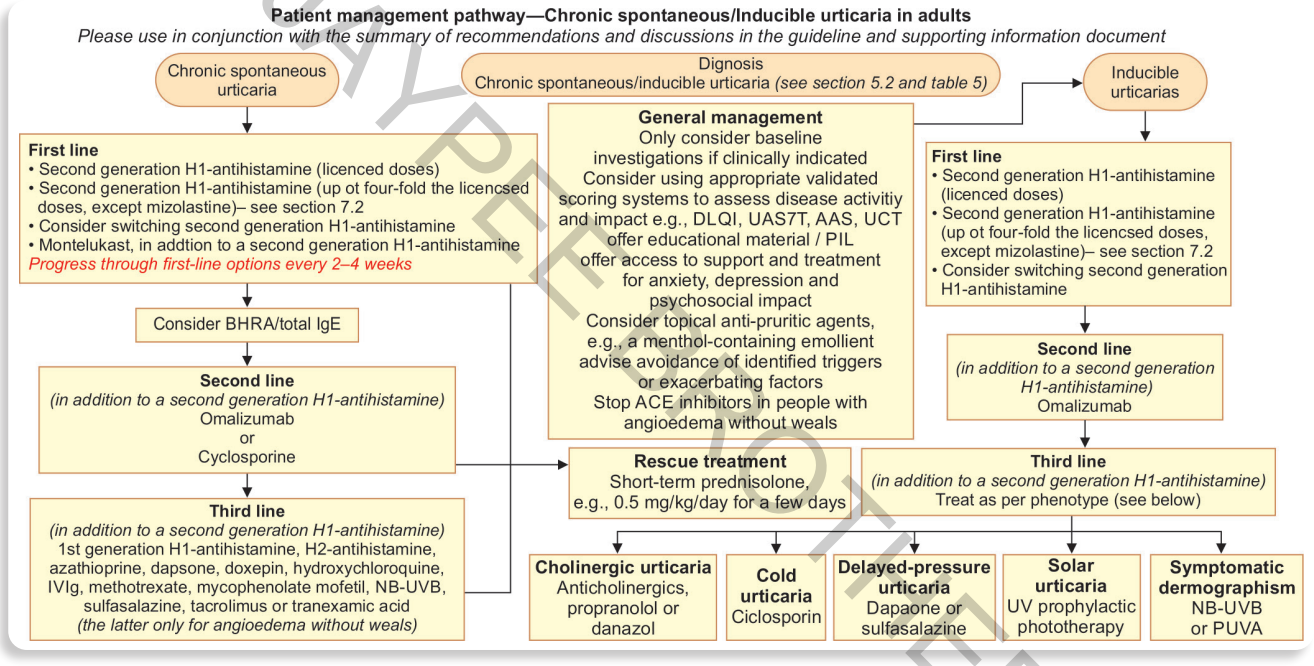


**Flowchart 4.1:** Patient management pathway for urticaria. For clarity we have divided management options into sections (general treatment, and first-, second-, and third-line options). However, depending on disease severity, disease fluctuation, comorbidities, and national criteria for use of drugs, the order and combinations of treatment may vary and change during each person's disease.

(AAS: angioedema activity score; ACE: angiotensin converting enzyme; BHRA: basophil histamine release assay; DLQI: dermatology life quality index; IVIg: intravenous immunoglobulin; NB-UVB: narrow band ultraviolet B; PIL: patient information leaflet; PUVA: psoralen plus ultraviolet A; UAS7: urticaria activity score summed over 7 days; UCT: urticaria control test)

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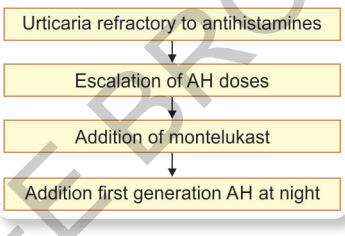
methods of treatment, such as combinations of modern second-generation H1-antihistamines with antileukotrienes, are based on clinical trials with low levels of evidence. Based on the level of evidence, the recommended third-line treatment options are limited.

- Ligelizumab, a new anti-IgE monoclonal antibody, claims to be more efficacious and needs less frequent administration than omalizumab.
- Dupilumab, monoclonal antibodies targeting the IL-5 pathway, and Bruton's tyrosine kinase inhibitors are all been investigated for CSU.
- Other potential targets include siglec-8 (an inhibitory receptor on mast cell and eosinophil), prostaglandin receptors, and C5a receptors.

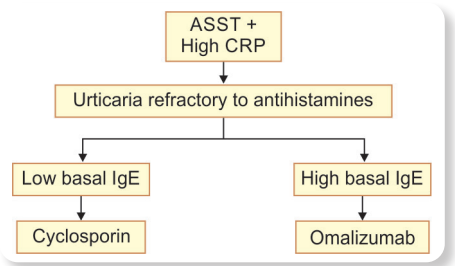
## *Urticaria Refractory to Antihistamines: Algorithm*




*Sources*:

1. AAAAI, ACAAI, & Joint Council of Allergy, Asthma, & Immunology 2014
2. Sabroe RA, Lawler F, Grattan CEH, Ardern-Jones MR, Bewley A, Campbell L, et al. Guidelines for the management of people with chronic urticarial. Br J Dermatol. 2022;186:398-413.

## *Urticaria Totally Refractory to Antihistamines: Algorithm*




*Source*: Sánchez-Borges M, Ansotegui IJ, Baiardini I, Bernstein J, Canonica GW, Ebisawa M, et al. The challenges of chronic urticaria part 1: Epidemiology, immunopathogenesis, comorbidities, quality of life, and management. World Allergy Organ J. 2021;14(6):100533.

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## Omalizumab (Anti-IgE)

***Omalizumab: Approval in urticaria***

Omalizumab has been approved in United States in 2014 for treatment of chronic idiopathic urticaria patients who do not respond to approved dose of H1-antihistamines in adults and above 12 years of age. The drug has been conditionally approved in India in same year in same indication.

- Omalizumab has been approved in United States in March 2014 for treatment of chronic idiopathic urticaria patients who do not respond to approved dose of H1-antihistamines in adults and above 12 years of age.
- The drug has been conditionally approved in India in October 2014 in same indication.
- 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. Omalizumab denotes a targeted therapy that binds to immunoglobulin E (IgE). It suppresses histamine-induced skin reactions, probably through its reduction of IgE and downstream effects on cellular activation mechanisms. Omalizumab is effective often independently from total serum IgE.
- Dose of omalizumab is 150 mg/300 mg every 4 weekly for 12–24 weeks by subcutaneous injection. Antihistamines or leukotrienes inhibitors may be coprescribed. Side effects are injection site reaction, infection (especially parasitic), thromboembolic events, headache, etc.
- Omalizumab (anti-IgE) has now been shown to be very effective in the treatment for CSU, both in case reports and case series as well as in double-blind placebo-controlled studies in antihistamine refractory selected patients. Omalizumab has also been reported (case reports and small series) to be effective in cholinergic urticaria, cold urticaria, solar urticaria, heat urticaria, symptomatic dermographism, and delayed pressure urticaria.
- Omalizumab should be considered for refractory CU if this is favorable from the standpoint of balancing the potential for benefit with the potential for harm/burden and cost and the decision to proceed is consistent with patients' values and preferences.

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