

Urticaria

Definition

Urticaria are edematous lesions with raised round or oval centers (wheals) of varying size and may occur anywhere on the body.



- The area surrounding the wheal is erythematous, well circumscribed, and blanches with pressure.
- Urticaria may coalesce and create an appearance of irregular margins, but lesions remain well defined.
- Urticaria is transient skin lesions that last for minutes to hours and resolve completely within 24 hours.

- Typical lesions are pruritic and are not associated with pain or burning sensations.
- Atypical urticaria lesions can be non-blanching, burning in character, last more than 24 hours, cause residual skin hyperpigmentation, bruising or scarring. These may represent vasculitic disease and warrant further evaluation.

How should urticaria be classified?

We **recommend** that urticaria is classified based on its duration as acute (≤ 6 weeks) or chronic (> 6 weeks).

↑ ↑

Strong
consensus¹

Expert
consensus

¹ $\geq 90\%$ agreement

We **recommend** that urticaria is classified as spontaneous (no definite eliciting factor involved) or inducible (specific definite factor involved).

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- The majority of urticaria cases are acute, lasting less than 6 weeks.
- Hives may occur in one isolated outbreak or hives may occur daily or almost daily for several weeks and then resolve.
- In 30% of patients, hives continue to occur on most days of the week for longer than six weeks and referred to as chronic urticaria.

- Wheal has three typical features:
 - A sharply circumscribed superficial central swelling of variable size and shape, almost invariably surrounded by reflex erythema
 - An itching or sometimes burning sensation
 - A fleeting nature, with the skin returning to its normal appearance within 30 min to 24 h.

Clinical Manifestations

- The primary clinical manifestation of urticaria is the symptom of **pruritus**.
 - Pruritus may disrupt sleep, causing fatigue.
 - Sometimes a burning sensation may accompany.
- Lesions can occur anywhere in the body and recover in approximately 2-3 h without leaving a trace. This spontaneous recovery can sometimes last up to 1 day.

Prevalence

- The lifetime incidence of urticaria is estimated to be 15-20%.
- Both genders
- All ethnicities.
- **Acute urticaria is more common in children and young adults.**

- **Chronic urticaria** affects 0.5-1% of individuals
- More common in adults
- More common in women.

Pathogenesis

- **The major effector cells of urticaria are mast cells, although basophils are also implicated.**
- **Mast cells are found in superficial dermis and sub-dermis in proximity of blood vessels as well as in mucosal surfaces of the mouth, nose, lungs, and digestive tract.**
- **The allergic response of hypersensitivity occurs when allergens cross-link IgE that is bound to high affinity IgE receptors (FcεR1) on the surface of mast cells which leads to mast cell activation.**

- The symptoms and signs of urticaria are due to multiple mediators that are released following activation of mast cells. Soon after activation of mast cells mediators such as histamine, leukotriene C4, leukotriene D, prostaglandin D2, as well as PAF are released.

- Histamine is released from preformed granules and is the primary contributor to hive formation. It leads to vasodilation and increased vascular permeability resulting in erythema and edema.
- Also, urticaria show a dense perivascular inflammatory cell infiltrate comprised of eosinophils, basophils, neutrophils, and CD4- and CD8-positive T-lymphocytes, similar to that seen in late phase reactions.

Etiology

- The causes of acute urticaria include
 - **Systemic allergic reaction,**
 - **Ingestion of allergens,**
 - **Skin contact with allergens,**
 - **Pseudo-allergic reactions**
 - **Toxic reactions**
 - **Viral infections.**

- **The most frequent IgE-mediated reactions that cause acute urticaria are allergic reactions to foods and to medications.**
- The **most common culprit foods** in children are
 - Milk
 - Eggs and
 - Peanuts,whereas in adults, peanuts, tree nuts, shellfish and fish are most common.

- **Medications:** Any drug may cause urticaria.
 - Antibiotics, most typically penicillin or cephalosporins, are commonly implicated medications in acute urticarial reactions.
- **Contact urticaria** occurs after direct skin contact with an allergen, such as urticaria that appears on the extremities after sitting on grass in a grass-allergic patient. Latex, cosmetics, and chemicals may also cause urticaria by contact.

- In addition to IgE-mediated allergic reactions to medications, some medications activate mast cells through IgE-independent pathways, called pseudo-allergic reactions.
- The most frequently implicated medications in these pseudo-allergic reactions are **NSAIDs, opioids, contrast and vancomycin**.
- **Acute urticaria can also occur during or following an inflammatory process such as viral illness, as frequently observed in children.**

- **Insect bites:** They should be questioned, especially in children.
- **Psychogenic factors:** Reasons such as stress, sadness, and depression may aggravate the preexisting urticaria and also induce urticaria.
- **Systemic diseases:** They may cause especially chronic urticaria. The presence of thyroid diseases and rheumatic diseases such as SLE, lymphoma, leukemia, and carcinomas may be investigated as required.

- **Physical factors:** Urticaria may develop due to external factors such as pressure, hot, cold, and dermographism.
- **Preservatives:** such as azo dyes, benzoic acid derivatives, and salicylates and food dyes are also important causative factors.
 - Urticaria is usually seen 1-2h after ingestion.
 - Food-related urticarial rashes are more common in children.
- **Hereditary:** Hereditary urticaria is seen in types of urticaria as angioedema and familial cold urticaria.
- **Idiopathic** urticaria without any known cause may be also seen.

- While most cases of acute urticaria can be identified by clinical history, approximately **75% of cases of chronic urticaria have no identifiable cause** and are classified as “idiopathic” or “spontaneous”.
- The remaining causes of chronic urticaria have specific physical triggers, most recently called “inducible” urticaria, to reflect that these lesions can be induced by specific physical stimuli and can be elicited with specific testing.

TABLE 6. Recommended classification of chronic urticaria

Chronic Urticaria Subtypes	
Chronic Spontaneous Urticaria (CSU)	Inducible Urticaria
Spontaneous appearance of wheals, angioedema, or both for >6 weeks due to known ^a or unknown causes.	Symptomatic dermographism ^b
	Cold urticaria ^c
	Delayed pressure urticaria ^d
	Solar urticaria
	Heat urticaria ^e
	Vibratory angioedema ^f
	Cholinergic urticaria
	Contact urticaria
	Aquagenic urticaria

- Physical stimuli activate mast cells by unknown mechanisms.
- Inducible urticaria/angioedema accounts for approximately 20% of chronic urticaria cases.
- The most common physical urticaria is dermatographism, in which scratching or stroking of the skin leads to acute wheal production.
- Dermatographism affects 2-5% of the population, with erythema and edema occurring about 10-20 min after applying mechanical trauma to skin.

Dermoglyphism

Many other physical stimuli have been reported for inducible urticaria, including :

- exercise,
- heat,
- cold,
- solar radiation,
- water,
- pressure, and
- vibration.

- Only about 5% of chronic spontaneous urticaria may have an identifiable cause.
- In rare cases, chronic urticaria is associated with comorbid infection, environmental exposures or hormonal changes or systemic illness.
- Appropriate management of these issues can result in resolution of urticaria.
- In endemic areas, infections with multicellular parasites such as strongyloides or filaria elicit a significant IgE response and may result in chronic urticaria.

- Exposure to foods, dietary supplements and medications may lead to chronic urticaria symptoms. However, the exposure must be frequent and would be considered a recurrent acute urticaria.
- Food and environmental allergy are uncommon causes of chronic urticaria, and there is a poor correlation with ingestion of suspected food triggers and provocation of urticaria in placebo controlled challenges.
- Contact allergens such as detergents and soaps, latex, hair or nail products, or other cosmetics may also cause contact hives.

- Some patients experience urticaria during menses or experience symptom flares during the menstrual cycle. These patients may have hypersensitivity to progesterone or autoimmune progesterone dermatitis.
- They may also have pseudo-allergic reactions to analgesics such as NSAIDs taken for menstrual symptoms.
- Urticaria may rarely be due to systemic autoimmune illness.

Diagnosis and evaluation

- Acute urticaria:
 - Due to the acute nature, a first episode of urticaria may occur **without an identifiable stimulus.**
 - Initial evaluation should focus on the clinical history, specifically **foods** and **medications** ingested within the hours preceding the appearance of hives.
 - It should also consider **dietary supplements** and **contact exposures, insect bites,** and **comorbid diseases.**
 - Recent history of a **viral infection** should also be elicited as a potential trigger, particularly in children.

- A trial of **discontinuation** of non-critical medications and dietary supplements should be considered, or medications changed to structurally unrelated compounds if possible.
- If food is suspected as a trigger, but a specific food cannot easily be identified, patients should be instructed to keep a retrospective food diary, recording all food up to 6 hours prior to each episode of urticaria.
- Even if no etiology is evident, management of the acute hives for the next several days or weeks is based on **symptomatic control, and no specific workup is required.**

Should routine diagnostic measures be performed in acute urticaria?

We **recommend against** any routine diagnostic measures in acute spontaneous urticaria.



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Chronic urticaria

- Spontaneous urticaria is characterized by hives that occur daily or almost daily for 6 weeks or more.
- **Chronic spontaneous urticaria is the most common type of chronic urticaria.**
- CSU was previously called “Chronic Idiopathic Urticaria”, but recent nomenclature has shifted to the term “spontaneous” to reflect that urticaria occurs spontaneously without an apparent trigger.
- This lack of an identifiable cause of urticaria is sometimes difficult for patient and health care providers to accept.

- Search for a cause of CSU can lead to **expensive**, potentially **invasive** and often **fruitless investigations**.
- The best diagnostic tool in the evaluation of CSU: **a thorough history and physical exam**, performed by a board certified specialist knowledgeable in urticarial disease.
- It is first best to **confirm that skin lesions are really hives**.
- It is important to ask the patients if they have **associated fever** with hive outbreaks, and if **lesions last >24 hours** or leave residual skin **discoloration**, as these features are atypical for chronic urticaria and suggest other diagnoses.

- Physical examination of the skin, lymph nodes, and abdomen for organomegaly is also important in the differential diagnosis of chronic urticaria.
- For the cases of chronic urticaria with a specific underlying cause, attention to physical triggers, foods, medications, supplements, contact exposures, autoimmune diseases and comorbid systemic illnesses is critical.
- If possible, medications which may cause pseudo-allergic reactions such as non-steroidal anti-inflammatory medications should be discontinued, and consideration should be given to stop all other non-critical medications and supplements.

Allergy testing

- While some patients with chronic urticaria will have positive skin tests to environmental allergens, there is little correlation between environmental aeroallergen skin test results and triggers of chronic urticaria.
- Environmental allergens do cause contact urticaria, which is acute in nature, but as they are not major causes of chronic urticaria, and environmental allergen testing is of low utility in the evaluation of chronic urticaria.

- Food allergens are often suspected but rarely implicated in the etiology of chronic urticaria.
- While up to 40% of patients suspect food as triggers of their chronic urticaria, foods are implicated as the cause of urticaria in food challenges in 5% or less of suspected cases.
- Neither environmental, nor food allergy testing is routinely recommended in the latest international practice parameter on evaluation and treatment of chronic urticaria.

- The role of thyroid autoantibodies in chronic urticaria is uncertain.
- Their presence may reflect a tendency of the patient to develop antibodies, but they may not play a direct role in chronic urticaria.
- Of patients with chronic urticaria, 35-40% have a positive **autologous serum skin test** result: if serum from these patients is intradermally injected into their skin, a significant wheal and flare reaction develops. Such patients frequently have a complement-activating IgG antibody directed against the α subunit of the IgE receptor that can cross-link the IgE receptor (α subunit) and degranulate mast cells and basophils.
- An additional 5-10% of patients with chronic urticaria have anti IgE antibodies rather than an anti-IgE receptor antibody.

Lab testing

- In patients with uncomplicated chronic spontaneous urticaria, it may be appropriate to refrain from performing a laboratory workup or to limit investigation to a CBC and CRP.
- Extensive laboratory investigations are unlikely to reveal a cause of urticaria and rarely lead to changes in management resulting clinical improvement in urticaria.

What routine diagnostic measures should be performed in chronic spontaneous urticaria?

We **recommend** limited investigations. Basic tests include differential blood count, CRP and/or ESR, and in specialized care total IgE and IgG anti-TPO, and more biomarkers as appropriate.

We **recommend** performing further diagnostic measures based on the patient history and examination, especially in patients with long-standing and/or uncontrolled disease.

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- Although routine laboratory testing in chronic urticaria is not necessary, selected laboratory testing may be indicated based on the history and physical examination.
- Examples:
 - If lesions are suggestive of urticaria pigmentosa, a skin biopsy with specific staining for mast cells can be performed.
 - If there is concern for mastocytosis, a serum tryptase may be obtained, and if significantly abnormal, a bone marrow biopsy is indicated.

- Any concern for carcinoid syndrome, should prompt a 24h urine level measurement of 5-HIAA.
- For concerns of lupus or porphyria screening involves testing for ANA and measuring total plasma porphyrin respectively.
- Although few patients with Hoshimoto's thyroiditis have urticaria, an increased incidence of elevated antibodies to thyroid peroxidase or thyroglobulin have been found in multiple studies of patients with chronic urticaria.
- A TSH may be checked in those with symptoms or signs of hypothyroidism, which could potentially be treated. However, the utility of checking a TSH in all chronic urticaria patients is controversial.

Treatment

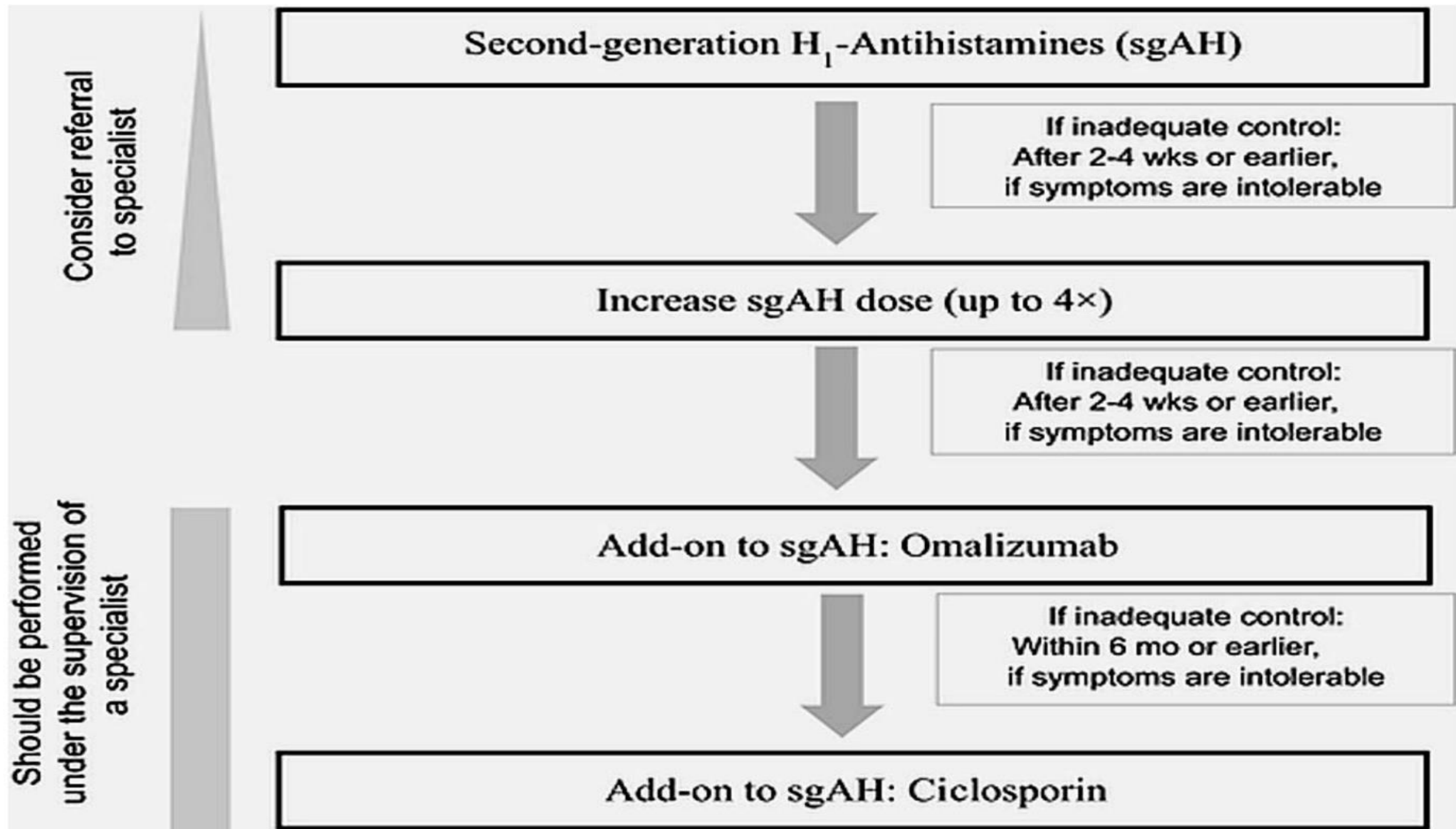
- Acute urticaria:
 - Typically self limited
 - Responds well to antihistamines (such as hydroxyzine and diphenhydramine causing sedation)
 - Second generation antihistamines such as fexofenadine, cetirizine, and loratadine are recommended as first line therapy with minimal or no sedation due to less morbidity across the BBB.
 - Third generation antihistamines (desloratadine, levocetirizine) can also be used.

- Superior results are achieved when these medications are taken on a scheduled basis and can block binding of histamine to the histamine receptor, rather than when they are taken to treat already existing hives.
- In some patients, it is useful to add a first generation antihistamine at night for breakthrough symptoms.
- Ketotifen is an antihistamine mast cell stabilizer and can also be used.
- NSAIDs and opioids should be discontinued, at least temporarily, in all patients with urticaria if medically tolerable.

- Chronic urticaria:
 - H1 receptor blocking antihistamines are the mainstay of chronic urticaria treatment, and second generation antihistamines are preferred first-line agents.
 - However, H1 antihistamines at standard doses may not control symptoms in 25-50% of people affected and a 4-fold increment in dosage may be needed.

- Increased doses of non-sedating, second generation antihistamines do not control symptoms in up to 50% of those with chronic urticaria.
- If this occurs, some guidelines suggest the addition of sedating first generation H1 antihistamines such as hydroxyzine or doxepin.
- As with acute urticaria, severe symptoms may require a course of systemic corticosteroids to control symptoms. However, the deleterious effects of chronic systemic steroids limit their use, and there have been few controlled studies in chronic urticaria.

- If refractory to antihistamines, international guidelines recommend initiation of omalizumab.
- If symptoms refractory to omalizumab, immunomodulatory therapy can be initiated, with the best evidence supporting use of cyclosporine.



Other treatments for antihistamine and omalizumab refractory chronic urticaria are:

- Hydroxychloroquine
- Sulfasalazine
- Dapsone
- Colchicin
- Azathioprine
- Cyclophosphamide
- Methotrexate
- Immunomodulators (mycophenolate, tacrolimus)

Prevention

Avoidance of

- triggers or minimization of trigger exposure
- Medications such as NSAIDs or opioids
- Vasodilatory activities such as exercising, showering with hot water or vasodilatory compounds such as alcohol
- Psychosocial stress

Prognosis

- For most patients with chronic urticaria, the prognosis is good to excellent, with 20-80% of patients experiencing spontaneous resolution within 1 year.
- Many patients may have persistent symptoms for >10 years.
- Some of those who experience resolution of symptoms, may experience recurrence later in life.
- Patients with physical urticaria, a component of pressure-induced urticaria or evidence of autoimmune associated urticaria tend to have more severe and persistent symptoms.

References

- The International EAACI/GA2LEN/EuroGuiDerM/APAAACI guideline for the definition, classification, diagnosis and management of urticaria Allergy 2022
- Textbook of Allergy for the Clinician 2021
- Nelson Text Book of Pediatrics 21st edition

