

## COMPREHENSIVE REVIEW ON URTICARIA: FROM ETIOLOGY TO EMERGING THERAPIES

Tejas Patel, Satyajit Sahoo\*, Sapna Desai, Sohan Patel, Vaishali Sharma, Arsh Jujara

Pioneer Pharmacy College, Vadodara, Gujarat, India – 390019

\*Corresponding Author's E mail: [satyajitppdc@gmail.com](mailto:satyajitppdc@gmail.com)

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### ABSTRACT

Urticaria is an inflammatory skin disorder that affects up to 20% of the world population at some point during their life. It presents with wheals, angioedema or both due to activation and degranulation of skin mast cells and the release of histamine and other mediators. Most cases of urticaria are acute urticaria, which lasts  $\leq 6$  weeks and can be associated with infections or intake of drugs or foods. Chronic urticaria (CU) is either spontaneous or inducible, lasts  $> 6$  weeks and persists for  $> 1$  year in most patients. CU greatly affects patient quality of life, and is linked to psychiatric comorbidities and high healthcare costs. In contrast to chronic spontaneous urticaria (CSU), chronic inducible urticaria (CIndU) has definite and subtype-specific triggers that induce signs and symptoms. The pathogenesis of CSU consists of several interlinked events involving autoantibodies, complement and coagulation. The diagnosis of urticaria is clinical, but several tests can be performed to exclude differential diagnoses and identify underlying causes in CSU or triggers in CIndU. Current urticaria treatment aims at complete response, with a stepwise approach using second-generation H1 antihistamines, omalizumab and cyclosporine. Novel treatment approaches Centre on targeting mediators, signalling pathways and receptors of mast cells and other immune cells. Further research should focus on defining disease endotypes and their biomarkers, identifying new treatment targets and developing improved therapies.

**Keywords:** Acute urticaria, chronic urticaria, hives, mast cells, antihistamines.

### INTRODUCTION

The term „urticaria “refers to any of a group of distinct skin conditions that are characterized by itchy, wheal-and-flare skin reactions (hives). In spontaneous urticaria, the most common type, the hives seem to arise without provocation. Spontaneous urticaria is divided into acute (lasting less than six weeks) and chronic types. The pathognomonic itching, hives, and angioedema arise by the same mechanism cutaneous mast cell activation and release of histamine and other mediators of inflammation in both acute and chronic urticaria, but these two disorders have different etiological profiles. The underlying cause of acute urticaria cannot be identified in about half of all cases. Chronic urticaria, which is much rarer, is usually caused by autoreactivity, chronic infection, or

intolerance to food additives. If the condition persists after the underlying cause has been treated or eliminated, non-sedating antihistamines are the agents of first choice for symptomatic treatment.

The most practical and most commonly used classification of urticaria ("hives") is based on the duration of its manifestations: acute urticaria (AU) resolves within six weeks, while chronic urticaria (CU) lasts longer than six weeks, and often for many years; CU may recur or persist steadily for decades<sup>1,2</sup>. Acute urticaria is between ten and one hundred times more common than chronic urticaria. In both types of "spontaneous" urticaria, the same typical manifestations (itching wheals and/or angioedema), appear at unpredictable times, often in sudden episodes. As a rule, neither the patient nor the treating physician can determine at first glance how and when an episode of urticaria has been induced ("spontaneous" urticaria). Most patients with certain other types of urticaria, however, know what factors induce their symptoms: physically induced urticaria, for example, might be brought about by cold, rubbing, or sunlight. Patients who know what factors induce their symptoms can prevent attacks by avoiding these factors. Inducible urticaria is said to be only one-third to one-half as common as spontaneous urticaria.

### Background:

Urticaria is among the most common dermatologic conditions presenting to the emergency department. A wide range of urticaria variants exist, including acute immunoglobulin E (IgE)–mediated urticaria, chemical-induced urticaria (non-IgE-mediated), autoimmune urticaria, cholinergic urticaria, cold urticaria, mastocytosis, periodic fever syndromes including Muckle-Wells syndrome, and many others.<sup>[1]</sup> While acute urticaria is generally related to an exogenous allergen or acute infection, chronic urticaria is more likely to be associated with autoimmunity<sup>2, 3</sup>.



**Figure 1: Urticaria Diseases (seen as rashes)**

Urticaria lesions may be mistaken for other pruritic or erythematous skin conditions such as atopic dermatitis, drug eruptions, contact dermatitis, insect bites, erythema multiforme, pityriasis rosea, and urticarial vasculitis. However, the diagnosis is typically clinical, based on the characteristic morphology of evanescent wheals (see the

images below), intense pruritus, and complete blanching on pressure (positive diascopy)<sup>4</sup>. Acute urticaria is most often a benign, self-limited skin condition. It typically occurs in isolation but can also be an early manifestation of anaphylaxis, contributing to more serious symptoms such as angioedema or anaphylactic shock. The causes of both acute and chronic urticaria are numerous, but an underlying trigger is more often identified in acute cases (40%–60%) than in chronic ones (10%–20%)<sup>5</sup>.

Lesions in IgE-mediated urticaria usually last less than 24 hours, are migratory, and resolve without residual skin changes. In contrast, urticarial vasculitis often presents with lesions that persist for more than 24 hours (though not invariably), tend to be both painful and pruritic, and may leave behind purpura or hyperpigmentation. Histologically, urticarial vasculitis shows evidence of leukocytoclastic vasculitis, distinguishing it from simple urticaria<sup>1,6</sup>.



**Figure 2: Urticarial vasculitis**

Urticarial vasculitis may occur with or without angioedema and is often associated with systemic symptoms such as arthralgias and gastrointestinal complaints, particularly in patients with hypocomplementemia. Unlike chronic spontaneous urticaria, it is more frequently associated with underlying autoimmune diseases (eg, systemic lupus erythematosus, Sjögren syndrome), infections, medications, or malignancy. If suspected, the diagnostic workup should include complement levels and a screen for autoimmune disease. Antihistamines may provide symptom relief, and NSAIDs are sometimes used cautiously; however, treatment often requires corticosteroids or immunosuppressants in more severe or systemic cases.

### **Classification of Urticaria:**

#### **"Spontaneous" urticaria**

Acute urticaria

Chronic urticaria

#### **Urticaria of physical origin**

Factitious urticaria

Cold urticaria

Solar urticaria

Delayed pressure urticaria

Vibration-induced urticaria

Heat urticaria

#### **Other types of urticaria**

Exercise-induced urticaria/anaphylaxis

Cholinergic urticaria

Contact urticaria

Aquagenic urticaria

#### **Pathogenesis of Urticaria:**

The main mechanism in the formation of urticaria is the release of various mediators from mast cells. Type 1 immunoglobulin (Ig) E-dependent hypersensitivity reaction is seen in acute urticaria. The antigen entering the body binds to specific antibodies on mast cells and basophils, causing the release of many mediators, primarily histamine. As a result, edema due to erythema and increased permeability secondary to vasodilatation <sup>6</sup>. Mast cells cannot be restimulated until regranulation after degranulation, which explains why the urticaria plate does not reappear for several days on the region. In chronic urticaria, the antigen entering the body binds to the IgE high affinity (FcεRIα) Fc receptor located on the mast cells and circulating basophils in the skin and degranulation from these cells occurs. When the same antigen is encountered for the 2<sup>nd</sup> time, these IgE antibodies that are already present on the mast cells and basophils immediately bind to the antigen and develop an allergic reaction more quickly <sup>7</sup>. This shows us that autoimmunity is also important in chronic urticaria.

The pathogenesis of urticaria is centered on the activation of cutaneous mast cells, which play a pivotal role in initiating the inflammatory cascade. Mast cells, located in the dermis and subepidermal tissue, degranulate upon activation and release a wide range of mediators, most notably histamine, but also leukotrienes, prostaglandins, cytokines, and chemokines. Histamine is the primary mediator responsible for the hallmark clinical features of urticaria: erythema, edema, and pruritus.

Following mast cell degranulation, histamine binds to H1 receptors in the skin, leading to vasodilatation and increased vascular permeability. This results in plasma extravasation into the dermis, forming the characteristic edematous wheals. At the same time, stimulation of sensory cutaneous nerves generates the intense pruritus associated with urticaria. Activated nerves also release neuropeptides such as substance P, which further amplify local inflammation and vasodilatation, leading to the “flare” or reflex erythema surrounding the wheal.

Both acute and chronic urticaria share these fundamental pathogenic mechanisms; however, their underlying triggers differ. In acute urticaria, mast cell activation is often transient and related to acute infections, allergens, or drug intolerance. In contrast, chronic urticaria is frequently associated with autoreactivity, such as the presence of autoantibodies directed against the high-affinity IgE receptor (FcεRI) or IgE itself, leading to recurrent and

sustained mast cell activation. Infections and pseudo allergic reactions to food additives may also serve as perpetuating factors in chronic cases.

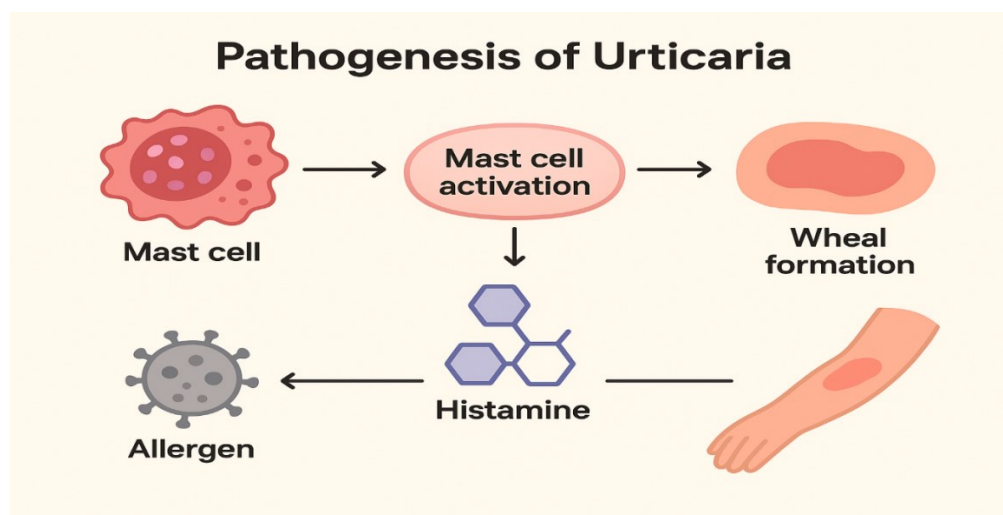


**Figure 3: Pathogenesis of urticaria.**

In addition to cutaneous manifestations, systemic effects can occur due to mediator release. Histamine and other inflammatory mediators may act beyond the skin, explaining the occurrence of extracutaneous symptoms such as headache, arthralgia, and gastrointestinal disturbances in some patients. Furthermore, in cases where individual wheals persist for more than 24 hours, urticarial vasculitis should be considered, as persistent wheals may represent immune complex-mediated vascular inflammation rather than simple mast cell-driven urticaria.

Overall, urticaria is the result of complex interactions between mast cells, immunoglobulins, complement factors, and neuropeptides. While histamine remains the central mediator, ongoing research highlights the involvement of autoimmune mechanisms and non-specific triggers that contribute to disease chronicity and variability in clinical presentation.

### Symptoms:

Symptoms include:

- Batches of welts, called weals, that can arise anywhere on the body.
- Welts that might be red, purple or skin-colored, depending on your skin color.
- Welts that vary in size, change shape, and appear and fade repeatedly.
- Itchiness, also called pruritus, which can be intense.
- Painful swelling, called angioedema, around the eyes, cheeks or lips.
- Flares triggered by heat, exercise or stress.
- Symptoms that persist for more than six weeks and recur often and anytime, sometimes for months or years.

**Clinical Feature of Urticaria: -****Acute urticaria: causes, diagnostic evaluation, and treatment**

The lifetime prevalence of acute urticaria lies between 10% and 25% <sup>4</sup>. This is thus one of the more common medical conditions known to man. In most cases, the symptoms are quite pronounced at first but then usually resolve within a few days or weeks. Most patients, therefore, speak of their ailment as occurring in "attacks" which they often attribute to an immediately preceding event, e.g., a stressful situation or the consumption of an unusual food or beverage. In fact, however, such precipitating factors play no role in the majority of cases of acute urticaria<sup>5</sup>: rather, the most common causes of acute urticaria in adulthood are acute infections (ca. 40%) and medication intolerance (ca. 10%). In childhood, infections account for up to 80% of cases of acute urticaria, but food allergies (e.g., against cow milk) are a more common cause than they are in adulthood <sup>6,7</sup>.

Because of the brief duration and self-limited course of a single attack of acute urticaria (remission within six weeks), an extensive search for its etiology is not indicated <sup>8</sup>. In particular, there is no indication for laboratory biochemical studies or for allergy testing. The exception to this rule is in severe cases of acute urticaria in which the history suggests a type I allergy as the cause; a prick test and, when appropriate, a measurement of specific IgE to identify the responsible allergen are indicated here so that further attacks can be avoided. In general, however, the main goal of the treatment of patients with acute urticaria is the complete suppression of the clinical manifestations. The treatment is therefore based on the extent, intensity, and duration of the symptoms and should be adapted to their further course. The most commonly used medications are modern, non-sedating antihistamines or glucocorticoids (both are given systemically), alone or in combination when necessary. Acute urticaria usually arises only once and does not progress to chronic urticaria <sup>9,10</sup>, though the rate of progression has been reported variously in the literature (from below 1% to 30%).

**Chronic urticaria: its causes and possible precipitating factors**

In the context of urticaria, the term "chronic" in its broad sense means nothing more than "lasting more than six weeks." In the current guidelines, however, the term "chronic urticaria" is restricted to apparently spontaneous cases and is thus used to distinguish these cases from physical and other types of urticaria <sup>11</sup>. Published estimates on the prevalence of CU vary considerably; typical figures from the German-speaking countries are in the range of 1% to 2% <sup>12</sup>. If this is so, then there are just over one million patients with CU in Germany. Women are affected about twice as often as men. Both typically develop the condition in the fourth to sixth decades of life.

The manifestations of CU may be present continuously or nearly every day (chronic continuous urticaria) or in the form of attacks separated by symptom-free episodes that may be as long as several weeks (chronic recurrent or intermittent urticaria). The condition persists for four years on average, but its duration in individual cases can range from 0 to 40 years <sup>13</sup>. Other authors, however, state that more than 50% of patients still suffer from CU ten years after their initial diagnosis <sup>14</sup>.

For these reasons, the treatment of chronic urticaria unlike that of acute urticaria is causally oriented with the intention of curing the condition, particularly when it has persisted for a long time or is very severe. Causally oriented treatment can only be provided, of course, when the underlying cause has been successfully identified <sup>15</sup>.

**Chronic urticaria due to infection: -**

It has long been known that chronic urticaria can arise as a response to chronic inflammatory, and particularly infectious, processes <sup>16</sup>. *Helicobacter pylori* infections of the gastrointestinal tract and bacterial infections of the nasopharynx (recurrent sinusitis and tonsillitis) appear to be the two major types of causative infection. Infections of the roots of the teeth can also cause urticaria. Pathological gastrointestinal microbes and parasites are a relatively rare cause of CU in Germany.

The importance of intestinal candidiasis is a controversial matter. The eradication of *Candida albicans* is recommended in patients with intense colonization or who manifest type I sensitization to this organism (grade D recommendation). The diagnosis of chronic urticaria due to infection should only be given when CU resolves completely, or at least improves markedly and lastingly, a short time after the eradication of the putatively causative infection.

**Chronic urticaria due to intolerance: -**

CU patients often themselves suspect that their urticaria is due to the previous intake of certain kinds of food. They might, indeed, suffer from CU because of food intolerance. The mechanism is not an IgE-mediated type I reaction to food, but rather a dose-dependent, usually delayed (4 to 12 hours) pseudo allergic reaction to food coloring, artificial flavoring, or preservatives <sup>17</sup>.

Chronic urticaria due to intolerance is diagnosed when

- after at least three weeks of strict adherence to a low-pseudo allergen diet, the manifestations of urticaria have improved by at least 50% (as documented in an "urticaria diary"), and
- provocative testing with food additives (through the intake of food high in pseudo allergens for 2 to 4 days) is seen to worsen the symptoms.

If the symptoms fail to respond to a low-pseudo allergen diet, the reason may be that the patient was not adhering to the diet strictly enough. Skin tests and laboratory studies are of no diagnostic value.

**Chronic urticaria of other causes: -**

About 10% of patients have urticaria due to other, much rarer causes, e.g., allergic urticaria (an entity that is much less common than generally thought) <sup>17</sup>, CU as a hormone-dependent event, or CU as a paraneoplastic phenomenon. No cause at all can be found in only a small minority of patients (less than 10% in specialized urticaria centers). Such patients are said to have CU of unknown cause.

Urticaria of whatever cause can be exacerbated or intensified by a large number of non-specific factors, e.g., stress, physical exertion, spicy or hot foods or beverages, flu-like infections, alcohol, acetylsalicylic acid and other non-steroidal anti-inflammatory agents, and angiotensin converting enzyme inhibitors.

**Autoreactive urticaria: -**

This type of urticaria is produced by mast cell activating substances that circulate in the blood. In at least some patients, the responsible substances appear to be autoantibodies directed against the IgE receptor FcεRI or against immunoglobulin E itself. A suspected diagnosis of autoreactive chronic urticaria can be easily confirmed with an autologous serum skin test (ASST). Serum is extracted from a freshly obtained specimen of whole blood and 50 µL of it is injected into the volar skin of the forearm. Normal saline and a histamine solution are injected simultaneously as negative and positive controls. The results of the test are then read off at 15 and 30 minutes.

The test reaction is said to be positive when the serum-induced wheal is greater than 2 mm in diameter, or more than 2 mm in diameter larger than the saline-induced wheal, if there is one. Some patients in whom positive tests are found do not have either of the two types of autoantibodies mentioned above, so that there must also be other serum factors for urticaria that have not yet been identified. Patients with autoreactive CU often have a high degree of urticarial activity in comparison with patients who have other types of CU. Nonetheless, their manifestations can usually be well controlled with symptomatic treatment in a sufficiently high dose.

**Etiology**

Many factors may be responsible in the etiology of the disease. Often, encountered factors include:

1. **Medications:** Any drug may cause urticaria. However, the most commonly encountered ones are penicillin, aspirin, nonsteroidal anti-inflammatory drugs, sulfonamides, thiazide diuretics, oral contraceptives, angiotensin-converting enzyme inhibitors, vitamins, codeine, morphine, curare and its derivatives, synthetic adrenocorticotrophic hormone, and radiocontrast substances. It may manifest from 1–2 hr to 15 days after oral intake. Urticaria related to the drugs given intravenously will occur immediately. While the drugs generally cause acute urticaria, they may cause emergence or exacerbation of CSU <sup>8,18</sup>.
2. **Foods:** Foods often encountered as causes of urticaria include nuts, eggs, fish, seafood, chocolate, meat, cow's milk, fruits (citrus fruits, grapes, plums, pineapples, bananas, apples, and strawberries), vegetables (tomatoes, garlic, onions, peas, beans, and carrots), mushrooms, fermented foods, spices, and spirits. Preservatives such as azo dyes, benzoic acid derivatives, and salicylates and food dyes are also important causative factors. Urticaria is usually seen 1–2 h after ingestion. Food-related urticarial rashes are more common in children <sup>9</sup>. Although it is accepted that foods have a place in the etiology of acute urticaria, their roles in the etiology of CSU have been not proven yet. It is thought that mostly pseudoallergens are involved in CSU, and therefore, diet is recommended for these patients <sup>10,19</sup>.
3. **Respiratory allergens:** Pollen, mold spores, mites, animal dandruff, and hairs may cause urticaria when taken through the respiratory tract <sup>11,20</sup>. Smoking is also an important factor since it contains many chemicals and can worsen the urticaria, hives should be advised to stop smoking. Urticaria caused by respiratory allergens usually occurs immediately after contact.

4. **Infections:** Respiratory infections such as sinusitis, tonsillitis, dental abscesses, urinary tract infections, hepatitis, infectious mononucleosis, and parasites may cause urticaria <sup>12,22</sup>. Parasitosis are the cause of urticaria, especially in children.
5. **Contact urticaria:** Latex, cosmetics, and chemicals may cause urticaria by contact <sup>13,23</sup>.
6. **Insect bites:** They should be questioned, especially in children <sup>14,24</sup>.
7. **Psychogenic factors:** Reasons such as stress, sadness, and depression may aggravate the preexisting urticaria and also induce urticaria <sup>15,25</sup>.
8. **Systemic diseases:** They may cause especially chronic urticaria. The presence of thyroid diseases and rheumatic diseases such as systemic lupus erythematosus, lymphoma, leukemia, and carcinomas may be investigated as required. It should be noted that urticaria may occur also in pregnant women <sup>11</sup>.
9. **Physical factors:** Urticaria may develop due to external factors such as pressure, hot, cold, and dermographism<sup>13</sup>. Urticaria secondary to pressure generally manifests an average of 3–4 h after exposure to pressure. Therefore, they are termed as delayed pressure urticaria.
10. **Hereditary:** Hereditary urticaria is seen in types of urticaria as angioedema and familial cold urticaria.
11. Idiopathic urticaria without any known cause may be also seen.

**Table 1: Summary of Evaluation and Diagnosis of Urticaria [27-32]**

| Aspect                               | Key Points                                                                                                                                                                                          |
|--------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Diagnosis</b>                     | Primarily clinical, based on detailed history and physical examination. Laboratory tests are limited and only used when specific causes are suspected.                                              |
| <b>Classification</b>                | <b>Acute urticaria:</b> lasts < 6 weeks. <b>Chronic urticaria (CU):</b> lasts > 6 weeks.                                                                                                            |
| <b>Duration of Individual Wheals</b> | Typical wheals last < <b>24 hours</b> . Lesions persisting > 24 hours suggest <b>urticarial vasculitis</b> .                                                                                        |
| <b>Main Symptoms</b>                 | Intensely pruritic (itchy) wheals, often worse at night, affecting quality of life. May be associated with angioedema.                                                                              |
| <b>Important History</b>             | Onset, duration, frequency of lesions, angioedema, systemic symptoms (fever, arthralgia, abdominal pain), and aggravating factors.                                                                  |
| <b>Medication History</b>            | Important to identify drug-induced urticaria. Common triggers: <b>NSAIDs, antibiotics, opioids, ACE inhibitors, antidepressants</b> . Reactions may occur months or years after starting treatment. |
| <b>Chronic Urticaria Causes</b>      | 80–90% are <b>idiopathic</b> . Many cases may be autoimmune in origin.                                                                                                                              |

|                                       |                                                                                                                                                               |
|---------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Associated Autoimmune Diseases</b> | Hypothyroidism, systemic lupus erythematosus (SLE), type 1 diabetes mellitus, and celiac disease. Autoimmune CU is often more severe and treatment-resistant. |
| <b>Malignancy Association</b>         | Rare, but <b>urticarial vasculitis</b> may be associated with systemic diseases and neoplasms.                                                                |
| <b>Physical Examination</b>           | Assess morphology, distribution, duration of wheals, presence of angioedema, and triggers such as cold, heat, pressure, or dermographism.                     |
| <b>Systemic Examination</b>           | Look for fever, lymphadenopathy, weight loss, arthritis, or other signs suggesting vasculitis or autoimmune disease.                                          |
| <b>Routine Investigations</b>         | Usually not required in chronic urticaria because most cases are idiopathic.                                                                                  |
| <b>Targeted Laboratory Tests</b>      | CBC, ESR, CRP, thyroid function tests, and autoimmune screening when clinically indicated.                                                                    |
| <b>Allergy Testing</b>                | Skin prick test or serum-specific IgE testing if Type I allergy is suspected. Food allergy is rarely a cause of chronic urticaria.                            |
| <b>Skin Biopsy</b>                    | Considered in persistent, atypical, or suspicious cases to exclude <b>urticarial vasculitis</b> .                                                             |

## TREATMENT

### Basic steps in the treatment:

Elimination of detectable etiologic causes and avoiding triggers constitute the first step of treatment. If the patient expresses that the lesions occur in any condition, such as after a drug or food intake, he must avoid this situation. If there is a noticeable infectious condition, it should be treated. In an important subgroup of patients with chronic urticaria, exacerbations triggered by physical stimuli occur. Training patients can help them avoid these stimuli or understand their symptoms. As an example, heat (hot showers and excessive humidity) is the common trigger of many people. Tight clothing or rubber bands may exacerbate symptoms. On the other hand, physical urticaria (dermographism, cold, hot, solar, cholinergic, pressure urticaria, etc.) developed with the stimuli of physical factors should be properly diagnosed and the stimulant should be eliminated <sup>33</sup>.

Many drugs, especially aspirin and nonsteroidal anti-inflammatory drugs, may worsen symptoms. It is best to stay away from these drugs during this period <sup>34</sup>. A 4-week elimination diet is recommended for pseudo allergens thought to induce urticaria. Alcohol consumption is not recommended <sup>35</sup>. Concomitant stress, sleep disturbance, infections, remonstration, and irregular antihistamine use may also aggravate the disease <sup>36</sup>. Rarely reported triggers

are cigarette smoke, house dust mites, pollens, molds, and spores, and the patient should be informed about all these possible irritants<sup>37</sup>. After warning the patient about these issues, it is necessary to control the symptoms by suppressing the mediator release as the second step of the treatment. In the treatment of urticaria (with or without angioedema), the focus should be on the immediate relief of pruritus and angioedema, if any. Approximately two-thirds of the cases of acute urticaria may be spontaneously confined and recover spontaneously.

### **H1 antihistamines:**

Antihistamines bind to histamine receptors and prevent the formation of pruritus and urticarial plaques<sup>38</sup>. The old generations of antihistamines are called the first generation and the new generations are called the second generation as follows:

First-generation agents (e.g., diphenhydramine, chlorpheniramine, hydroxyzine, cyclizine, dimenhydrinate, doxepin, doxamine, meclizine, promethazine, etc.)

Second-generation agents (cetirizine, loratadine, fexofenadine, desloratadine, levocetirizine, ebastine, and bilastine).

In the treatment, the second-generation H1 antihistamines are preferred. The first-generation H1 antihistamines are less preferred due to their significant sedation and side effects and short duration of action<sup>39</sup>. Antihistamines should be used on a daily basis but not in case of need. There is not yet sufficient data to suggest the most effective antihistamine in the treatment of CSU. The response to antihistamines and the possible side effects may vary from person to person. The second-generation agents are more often preferred for both adults and children due to their low side effects, less drug-drug interaction, anticholinergic effects, longer duration of action, and higher safety<sup>40</sup>. Some patients may need higher dosages (up to 4 times) than standard doses for the control of urticarial symptoms and may experience drowsiness and sedation as side effects at high doses.

### **H2 antihistamines:**

Combination of H1 and H2 antihistamines may be more effective for acute urticaria than H1 antihistamines alone. However, the use of H2 in recent years has been removed from some guidelines<sup>41</sup>. H2 antihistamine options include ranitidine, nizatidine, famotidine, and cimetidine; however, cimetidine may increase levels of other drugs so it should be used with caution.

### **Systemic corticosteroids:**

Glucocorticoids do not inhibit mast cell degranulation, but they probably act by suppressing various inflammatory mechanisms. Glucocorticoids are not considered necessary for isolated urticaria. However, systemic glucocorticoids should be considered in cases with significant angioedema or if the symptoms persist for more than a few days and cannot be controlled by antihistamines. To control persistent and severe symptoms, systemic glucocorticoids may be added to antihistaminic therapy for a short period of time<sup>42</sup>. In adults, prednisone is given for an average of 5–10 days at daily doses of 30–60. In children, daily dose of prednisolone is 0.5–1 mg/kg (maximum 60 mg/day) which is tapered and discontinued within 5–7 days.

**Cyclosporine:**

Compared with systemic corticosteroids, cyclosporine (5 mg/kg/day) has been reported to cause a more rapid and long-term remission. Clinical response rates are between 64% and 95%. When the duration of the treatment is completed, 50% of the patients may have remissions up to 9 months, but in some patients, relapses may occur after discontinuation of the treatment. In this case, maintenance therapy can be maintained at doses of 1.5–2 mg/kg/day for up to 2 years. The longer the duration of use, the higher the risk of side effects. It is used as an off-label drug for the treatment of CSU<sup>24</sup>. Although cyclosporine is a highly effective agent in the treatment of CSU, it should be preferred in patients with chronic urticaria resistant to high-dose antihistamines and omalizumab treatment, especially due to the risk of side effects that may occur during long-term use<sup>43</sup>.

**Omalizumab:**

Omalizumab, a monoclonal antibody (anti-IgE IgG) against IgE, is safe and effective for many patients, but it is too expensive and does not appear to have long-term disease-improving effects. Omalizumab reduces mast cell function and induces eosinophil apoptosis. It reduces cytokine release from basophils and migration of immune cells to tissue<sup>44</sup>. There are no studies directly comparing omalizumab with other treatments for resistant chronic urticaria.

There is no need for laboratory tests before and during the treatment. It is administered subcutaneously at a dose of 300 mg every 28 days for 6 months. It is effective in >80% of the patients. Omalizumab has also been reported to be effective in the treatment of other forms of urticaria, such as cold urticaria, solar urticaria, cholinergic urticaria, symptomatic dermatographic, and urticarial vasculitis. Omalizumab is the only approved, effective, and reliable treatment option for CSU patients with persistent symptoms despite high-dose antihistamine therapy. In case of recurrence after 6 months of use, it can be used again without loss of efficacy<sup>45</sup>.

**Leukotriene receptor antagonists (LTRAs):**

Zafirlukast and montelukast have not been studied in the treatment of acute urticaria. There is no double-blind, placebo-controlled study with LTRAs. Systematic reviews indicate that they are more effective than placebo, but they are not highly recommended except for aspirin-induced urticaria cases<sup>46</sup>.

**Treatment of urticaria in children:**

New generation H1 antihistamines are recommended as the first choice in the treatment of urticaria as long-term safety profiles are better. The first-generation H1 antihistamines should not be used because they have strong sedative effects and decreased psychomotor ability of the children. Antihistaminic doses can be increased up to 2 times by taking the body weight of the children into account in cases refractory to standard doses<sup>47</sup>.

There are no sufficient data on the use of LTRAs, cyclosporine, and omalizumab in the treatment of urticaria in children. Based on the treatment of adult urticaria, these agents may be used in addition to antihistamines in the third step of treatment. Evidence for the effectiveness and safety of omalizumab is increasing in children over 7 years of age. Pediatric patients who very well tolerated to monthly doses of 150–300 mg have been reported in the literature<sup>48</sup>. Cyclosporine has been used in children who are unresponsive to antihistaminic therapy as in adults

and has been found to be highly effective. Systemic corticosteroids can be used for a maximum of 10 days in pediatric patients experiencing angioedema attacks or widespread severe urticaria.

#### **Treatment of urticaria during pregnancy and lactation:**

In the latest treatment guidelines, it is stated that the classical treatment algorithm proposed in the treatment of urticaria in pregnancy can be applied. The pregnancy category B is indicated for chlorpheniramine, loratadine, cetirizine and levocetirizine is the pregnancy and category C for all other antihistamines. Immediate use of the first-generation H1 antihistamines with sedative effect has been found to be inconvenient as it causes respiratory depression in the infant. All current guidelines emphasize that new generation antihistamines are more reliable in the treatment of urticaria in pregnant patients <sup>49</sup>.

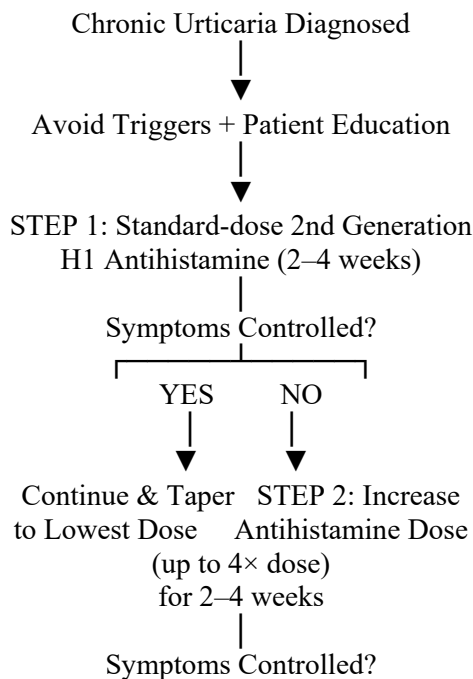
Pregnancy categories B and C are, respectively, assigned for LTRAs and cyclosporine.

There is no experience in the use of omalizumab in pregnancy. While using omalizumab, 169 pregnancies were reported in asthmatic patients, without increase in major anomalies. The FDA classified omalizumab in pregnancy category B <sup>50</sup>. Loratadine and cetirizine may be preferred during the breastfeeding period because they are found in very low amounts in breast milk <sup>51</sup>.

#### **Other treatments: -**

The studies performed on the effectiveness of anti-inflammatory drugs such as dapsone, sulfasalazine, hydroxychloroquine, and colchicine, and studies on the effectiveness of immunosuppressive drugs such as methotrexate, mycophenolatemofetil, azathioprine, tacrolimus, mizoribine, and cyclophosphamide have low level of evidence <sup>52</sup>.

#### **Flowchart of Treatment algorithm for urticaria**



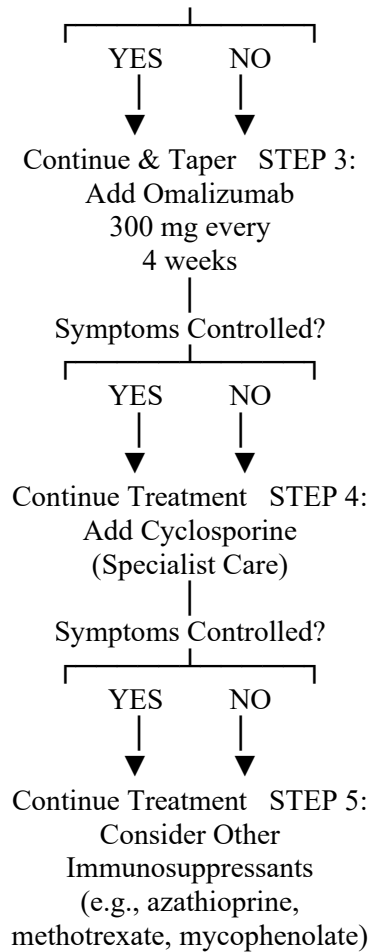
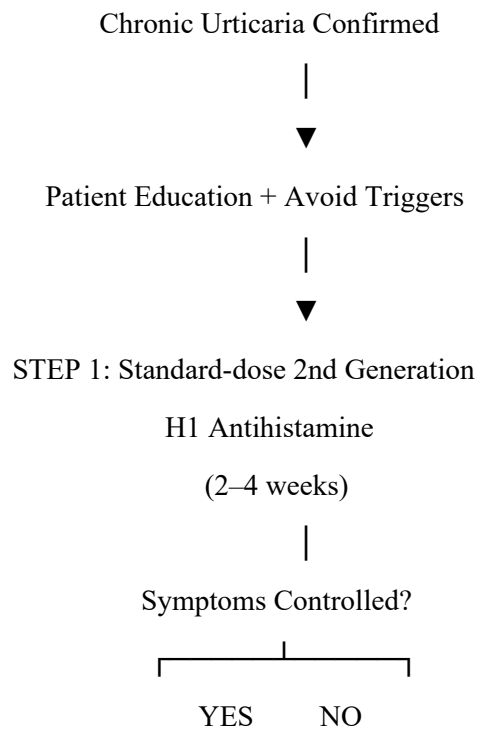
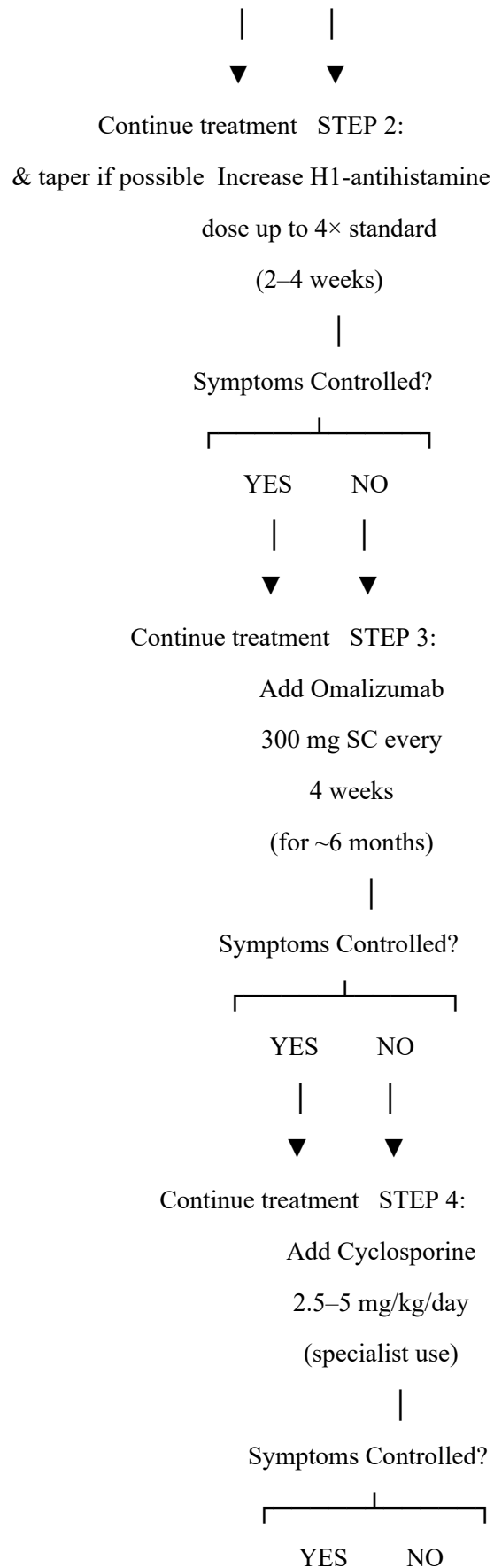


**Figure 4: Flowchart of Treatment algorithm for urticaria recommended by EAACI, GA2LEN, EDF, WOA**

**Flow Chart no. 2**





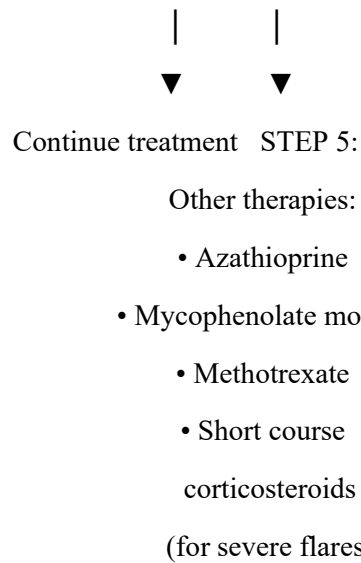


**Figure 5: Simple Turkish Guideline Treatment Algorithm for Chronic Urticaria**

#### **DRUG INDUCED URTICARIA: -**

Drug-induced urticaria is the term used when urticaria is caused by a drug, most often penicillin, a non-steroidal anti-inflammatory agent (NSAID), or sulfamethoxazole in combination with trimethoprim (see Sulfa drugs and the skin). The drug may be ingested or applied to the skin surface (contact urticaria).

The clinical features and treatment for drug-induced urticaria are identical to those for urticaria not related to drugs. It can be associated with angioedema, anaphylaxis, and serum sickness.

#### **Drugs that are known to cause urticaria:**

Drugs that are known to cause urticaria are listed below. The drugs marked with an asterisk (\*) are strongly associated with urticaria.

- Angiotensin-converting enzyme inhibitors (ACEIs)\*
- Antibiotics: penicillins\*, cephalosporins\*, macrolides (erythromycin), aminoglycosides, tetracyclines\*, sulphonamides, vancomycin, fluoroquinolones
- Anticoagulants: low molecular weight heparin, protamine sulfate
- Anticonvulsants
- Oral antifungal agents: fluconazole, ketoconazole, griseofulvin\*
- Antineoplastic agents: alkylating agents, taxanes, methotrexate
- Betadine (povidone-iodine)
- Bisphosphonates
- Dextran
- Dextromethorphan
- Enzymes: trypsin, streptokinase, chymopapain

- Hydantoins
- Hydralazine
- Mannitol
- Muscle relaxants: atracurium, vecuronium, succinylcholine, curare
- NSAIDS\*: ibuprofen, naproxen, diclofenac
- Opioids: morphine\*, codeine\*, meperidine, fentanyl• Paracetamol
- Polypeptide hormones: insulin, corticotrophin, vasopressin
- Progesterone
- Quinidine
- Radiographic contrast agents\*
- Salicylates\* including aspirin
- Sorbitol complexes
- Corticosteroids
- Thrombolytics: alteplase, urokinase
- Vaccines

## DISCUSSION

Urticaria represents a heterogeneous group of disorders characterized by the sudden appearance of transient wheals, angioedema, or both, resulting from mast cell and basophil activation with subsequent release of histamine and other mediators. Despite being one of the most common dermatological conditions, affecting up to 25% of individuals at least once in their lifetime, its etiology and management remain complex and multifactorial as per Zuberbier et al., 2021.

The discussion of urticaria must consider both **acute** and **chronic forms**, as they differ in underlying causes, prognosis, and therapeutic approaches. Acute urticaria is most often self-limiting and triggered by infections, medications, or food allergens, while chronic urticaria (CU) persists beyond six weeks and is frequently associated with autoimmune mechanisms, physical triggers, or remains idiopathic in a large proportion of cases.

A major challenge in CU is the identification of causative or exacerbating factors. Although laboratory investigations and allergy testing are generally unnecessary in acute urticaria, they may be considered in chronic or severe cases, especially when an autoimmune association is suspected. Importantly, CU has been linked to autoimmune thyroid disease, systemic lupus erythematosus, and other systemic conditions, highlighting the need for a comprehensive clinical evaluation. However, in 80–90% of cases, no clear trigger can be identified, which underlines the idiopathic nature of the condition.

From a therapeutic perspective, international guidelines consistently recommend second-generation, non-sedating H1-antihistamines as the first-line treatment due to their favorable safety and efficacy profile, 2021). In cases unresponsive to standard dosing, up-dosing up to fourfold is advised. For refractory cases, biologics such as omalizumab, an anti-IgE monoclonal antibody, have revolutionized management and demonstrated excellent

efficacy in randomized controlled trials. Other immunomodulatory agents such as cyclosporine may be considered in highly resistant cases, though side-effect profiles limit widespread use.

The psychosocial burden of chronic urticaria cannot be underestimated. Patients frequently report sleep disturbances, reduced work productivity, and impaired quality of life, often disproportionate to the objective severity of the disease. Stress and psychological comorbidities, in turn, exacerbate urticarial symptoms, creating a vicious cycle. Hence, management should also involve patient education, reassurance, and psychosocial support. Despite substantial progress, important gaps remain. The exact immunological pathways underlying idiopathic CU remain incompletely elucidated. While autoimmune theories dominate current research, the role of microbiome alterations, environmental exposures, and genetic predispositions are emerging areas requiring further study. Moreover, long-term safety data for biologic therapies are still limited, warranting careful post-marketing surveillance.

In summary, urticaria exemplifies the intersection of immunology, dermatology, and psychosomatic medicine. Effective management requires not only pharmacological intervention but also recognition of comorbidities and patient-centered care. Future advances in biomarker discovery and personalized medicine approaches may allow for stratified treatment algorithms, improving outcomes in patients with refractory disease.

## CONCLUSION:

Urticaria is an acute and chronic itchy rash that can be quite irritating. Angioedema may accompany urticaria, and rarely, it may be fatal. Although many etiologic factors such as infections, drugs, and foods are blamed in their etiology, they are often idiopathic. In the treatment of patients, if there is a detectable etiologic or trigger factor, it should be avoided and the patient should be warned for the possible existence of physical urticaria. Although antihistamines are used in the first step treatment, a wide variety of agents have been used, including corticosteroids, omalizumab, and cyclosporine. In medicine, there is no disease, there is a patient, and every patient should be treated with appropriate care. Nevertheless, it should be kept in mind that it is still a challenging disease for both the patient and the physician.

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