Update of the diagnosis and treatment of urticaria: Iranian Society of Dermatology clinical practice guideline

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Urticaria is a frequent and difficult-to-treat skin condition, described as temporary erythematous, raised, and itchy skin lesions (wheals) brought on by dilated blood vessels, elevated local blood flow, and increased vascular permeability. It can occur alone or in conjunction with angioedema. Urticaria can be diagnosed and treated in fields other than dermatology; patients often visit general physicians, internal medicine specialists, allergologists, and clinical immunologists. In 2018, the Iranian Society of Dermatology produced a clinical practice guideline on diagnosing and managing urticaria. To update the guideline, the Guideline Development Committee conducted an exhaustive search of scientific papers published on the topic from April 2018 to the end of August 2022, and the new guideline was developed. Finally, the updated guideline was critiqued by members of the Dermatology Board Certificate Examination Panel and chairs of dermatology departments in Iran, and it was improved using their feedback.

Keywords: urticaria, diagnosis, management, antihistamines, clinical guideline

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INTRODUCTION

Urticaria is a frequent and difficult-to-treat skin condition. Urticaria affects 1% to 5% of the general population. Urticaria treatment is not confined to dermatologists; general practitioners, allergologists, and clinical immunologists often treat urticaria patients. The Iranian Society of Dermatology aims to establish ways to provide the best possible care to people suffering from dermatological disorders. To accomplish this goal, the society formed a committee to seek and critically evaluate recent research findings and available recommendations to create a clinical practice guideline for diagnosing and treating urticarial [1,2]. As stated in the guideline,

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it was necessary to update it due to new information becoming available over the last four years.

METHODS

Methodology

The following tasks were completed to update the guideline:

1. Topic identification: Urticaria has a high incidence rate and poses major issues for sufferers. Keeping physicians updated on novel diagnostic techniques and treatments, depending on the availability of such techniques and therapies in Iran, may improve the services provided to urticaria patients. As a result, the topic "urticaria," including both spontaneous and chronic disease, was chosen.

2. The intended audience: Dermatologists in Iran are the primary target audience for this clinical practice guideline.

3. Agenda: An expert group of Iranian Society of Dermatology members revised the previous clinical guideline on managing urticaria. The panel included dermatology and skin disorders research center faculty members. The panel was responsible for scheduling meeting sessions and carrying out the actions required to create the revised guideline.

4. A systematic review of the relevant medical literature was conducted: The first stage was to search the PubMed electronic database from April 2018 to the end of August 2022, using "urticaria," "guideline," "systematic review," and "clinical trial" as keywords and "title/abstract" as the search filter. Eighty-eight publications were chosen from 156 retrieved titles and abstracts to update the guideline.

5. Creating the guideline: The Guideline Development Committee was given tools to monitor the clinical practice guideline development progress. All committee members commented on the guideline parts presented, and feedback was received by the members in charge of each section.

6. Accreditation: The revised guideline was distributed to dermatological Board Certificate Examination Panel members and chairs of dermatological departments throughout Iran, and it was altered in response to their feedback.

7. Publication: The Persian and English versions of the guidelines will be published in "Dermatology and Cosmetic" and "Iranian Journal of Dermatology," respectively. Both periodicals are widely distributed among Iranian dermatologists, who are the primary target audience for this recommendation.

8. Update: An expert panel was created to revise the guideline every three years. The guideline discusses the definition, classification, etiology, and pathophysiology of urticaria, as well as practical aspects relevant to the diagnosis and management of urticaria.

Definition

Urticaria is characterized as erythematous, elevated, and pruritic skin lesions (wheals) that are temporary alone or in conjunction with angioedema due to blood vessel dilation and increased local blood flow and vascular permeability. Lesions feature three distinct aspects:

1. The size of each lesion can range between a few millimeters and the size of a palm.
2. It is followed by pruritus and, in some cases, irritation.
3. It is transitory; the skin returns to normal after 30 minutes to 24 hours.

Urticaria can be seen alone or in groups.

Angioedema is caused by increased vascular permeability and mostly affects the lips, mouth, throat, eyelids, and genitalia, with three distinct aspects:

1. Swelling in the hypodermic layer, subcutaneous tissue, or mucous membranes that is red or skin-colored.
2. Tingling, irritation, stiffness, and even pain are more common than pruritus.
3. Wheal lesions are eliminated more slowly (up to 72 hours) [3,4].

Clinical classification

Urticaria's causal agent is challenging to identify. It appears that categorizing urticaria based on clinical symptoms is more convenient. The clinical classification of urticaria/angioedema is summarized in Table 1 and discussed below:

1. Spontaneous urticaria is the most frequent type, characterized by the abrupt emergence of skin lesions in any body region. It can arise on its own or in conjunction with angioedema. Ordinary urticaria usually appears abruptly and unexpectedly; however, exacerbating variables such as heat or garment pressure are recognized in most cases. Chronic urticaria is defined as urticaria with or without angioedema lasting longer than six weeks. Ordinary urticaria is defined

Table 1. Clinical classification of urticaria

Spontaneous urticaria
Acute (up to 6 weeks of continuous activity)
Chronic (6 weeks or more of continuous activity)
Episodic (6 weeks of intermittent activity; each outbreak less than 6 weeks)
Physical urticaria (induced by physical stimulation)
Inducible urticaria (induced by physical stimulation)
Delayed pressure urticaria
Symptomatic dermographism
Vibratory angioedema
Thermal cholinergic urticaria
Cold contact urticaria
Heat contact urticaria
Aquagenic urticaria (caused by exposure to water)
Solar urticaria
Exercise-induced anaphylaxis
Angioedema without urticaria
Known causes:
Drug-induced
C1 esterase inhibitor deficiency
Contact urticaria (contact with allergens or chemicals)
Urticarial vasculitis (skin biopsy shows vasculitis changes)
Autoinflammatory syndromes
Hereditary periodic syndromes associated with cryopyrin (CIASI mutations, acquired Schnitzler syndrome)

as acute urticaria with or without angioedema that lasts a few hours to a few days and recurs over time (months to years). Even though chronic urticaria is rarely life-threatening, it can cause major problems for the patient and diminish the patient's quality of life, making it equivalent to cardiovascular disease.

2. Inducible urticaria, as opposed to spontaneous urticaria, is produced by exposure to one or more physical irritants. If the triggering factors are recognized, altering the patient's lifestyle may minimize the amount of urticaria episodes or prevent them altogether. Among the most common causes of physical urticaria are mechanical and temperature forces. Symptoms are similar in children and adults. A patient may experience two or more forms of hives at the same time.

3. Angioedema without urticaria should be distinguished from urticaria-associated angioedema. The former can develop due to a lack of C1 esterase inhibitor enzyme or the use of angiotensin-converting enzyme (ACE) inhibitors. Angiotensin II type 1 receptor blockers, dipeptidyl peptidase IV inhibitors, and penicillins are less likely to cause angioedema. Patients may have abdominal pain without exhibiting obvious angioedema.

4. Contact urticaria develops only when allergens are absorbed through the skin or mucous membranes. Contact urticaria never happens on its own. Allergen absorption through the skin or mucous membranes can cause local or systemic hypersensitivity reactions. Contact urticaria may result in anaphylaxis in persons with hypersensitivity, such as those with severe allergic reactions to latex.

5. Urticarial vasculitis features lesions that clinically resemble common urticaria but are caused by the inflammation of tiny vessels, which can be seen under a microscope. Wheal lesions typically persist long, can be painful rather than itchy, and can leave a bruise or hyperpigmentation after inflammation. It can be difficult to distinguish urticarial vasculitis from delayed pressure urticaria. Urticarial vasculitis may indicate a systemic disease and be related to renal and joint issues. To confirm the diagnosis, a skin biopsy is required [3,4].

Auto-inflammatory syndromes

Urticaria is frequently linked with fever, malaise, and other systemic symptoms in auto-inflammatory disorders.

1. Cryopyrin-associated periodic syndrome (CAPS) often manifests in childhood, although there is also a late-onset acquired variety. CAPS comprises three concurrent conditions: familial cold autoinflammatory syndrome, Muckle-Wells syndrome (sensorineural hearing loss and renal amyloidosis), and neonatal-onset multisystem inflammatory disorder.

Hereditary instances are most common in childhood.

2. Schnitzler syndrome is relatively uncommon, and is distinguished from CAPS by organ involvement patterns. This syndrome is frequently accompanied by fever, tiredness, and elevated inflammatory markers [5].

Disease burden

Chronic urticaria significantly strains sufferers, their families, friends, the healthcare system, and society; it affects people's performance and sense of health. According to O'Donnell *et al.* [6], the impact on people with chronic urticaria's quality of life is comparable to those with coronary artery disease. Furthermore, patients with chronic urticaria have an inferior health status and satisfaction than healthy people and patients with respiratory allergies. Finally, the cost of treating persistent urticaria is high for both patients and society [6].

Etiology

A thorough grasp of the clinical symptoms, etiology, causes, and aggravating factors is required to manage acute and chronic intermittent urticaria effectively. Despite substantial research, the cause of chronic urticaria remains unknown in 40% to 50% of cases classified as idiopathic. Chronic urticaria patients are frequently classified as clinical cases of allergies, most likely related to food allergies, and efforts are made to pinpoint the allergens. However, dietary allergies do not cause chronic urticaria in most individuals and can typically be ruled out based on the patient's medical history. The most prevalent reasons for chronic urticaria recurrence are viral infections and, in certain circumstances, stress. The classification of chronic urticaria/angioedema based on the etiology of the disease is presented in Table 2 [3,4].

Pathogenesis

Despite comprehensive investigations, a specific cause cannot be detected in many cases of urticaria; however, some specific causes can be pointed out. Skin or mucosal mast cells are the major cells involved in urticaria. As a result of mast cell degranulation, vasoactive substances such as histamine are released. Histamine is known as one of the major compounds associated with the occurrence of urticaria and

Table 2. Etiological classification of urticaria/chronic angioedema

Etiology	Mechanism	Examples	Investigations
No known cause (40– 50% of cases)		Unknown	
Autoimmune	IgG autoantibodies against IgE receptors on mast cells or binding of IgE to mast cells	Associated with autoimmune inflammation of the thyroid gland	ANA, thyroid autoantibodies, autologous skin test (only for research purposes)
Physical stimuli	Direct release of chemical mediators from mast cells	Physical exercise, heat, cold, pressure, water, sun exposure, dermographism	Challenge tests with appropriate stimuli, such as ice, physical exercise, etc. Cryoglobulin
Drug-induced	Reduction in the metabolism of quinine, changes in leukotriene levels	ACE inhibitor (for angioedema alone), NSAIDs	Recovery by stopping drug use (may take weeks or months)
Infection	Activation of the complement and immune complex formation	Parasites, EBV, hepatitis B and C, other viruses	Serology based on clinical history
Allergy	IgE-mediated allergic contact urticaria	Latex, animals, grass, food	Skin test, allergen-specific IgE
C1 inhibitor deficiency	A) Hereditary B) Acquired	A) Type I and II hereditary B) Paraproteinemia-associated angioedema	C1, C4 inhibitors
Non-IgE mediated mast cell degranulation	Non-mediated	Drugs, ACTH	Non-contact recovery
Vasculitis	Inflammation of small blood vessels, deposition of immunoglobulins and complements	Urticarial vasculitis	ESR, CBC, renal Function tests, urine analysis, liver function tests, serological diagnosis of hepatitis B and C, immunoglobulin electrophoresis, screening for autoimmune diseases, ANCA, C3, skin biopsy
Lymphoproliferative disorders	Paraproteinemia	B-cell lymphoma	Paraprotein in blood and urine
Food additives (rare)	Unknown	Salicylates	Stopping exposure to allergen is effective

angioedema. Other mediators, such as leukotrienes and prostaglandins originating from the cell membrane, are released and react in superficial tissues during the initial and final reactions. Some characteristics of the activated mast cells, such as swelling and pruritus, are easily identifiable and usually respond to antihistamines. However, inflammation in the deeper layers of the skin is more difficult to identify, and more mechanisms are likely to be implicated. Various inflammatory agents increase capillary permeability, which induces plasma leakage and causes edema. Perivascular infiltration of CD4+ lymphocytes, monocytes, and granulocytes (neutrophils, basophils, and eosinophils) are seen in autoimmune urticaria and idiopathic chronic urticaria lesions. This contrasts with samples from patients with urticarial vasculitis (less than 1%) showing only small-vessel vasculitis, generally due to immune complex development. In certain situations, only minor alterations such as endothelial cell inflammation, red blood cell extravasation, and white blood cell infiltration are observed [3,4].

Immunologic urticaria

1. Autoimmune urticaria: Histamine-releasing autoantibodies are present in at least 30% of patients with idiopathic chronic urticaria. Adults and children with chronic urticaria have IgG antibodies against IgE receptors on mast cells in 40-60% of cases.

2. Immune complex-associated urticaria: Urticarial vasculitis and drug-induced urticaria (including serum sickness induced by blood products) are thought to be generated by the production of immune complexes in blood capillaries. Histamine release from mast cells is increased by complement activation via C5a anaphylatoxin. Antigen-antibody interactions and the creation of immune complexes are triggered by hepatitis B, hepatitis C, EBV, other viral diseases, and some parasite illnesses, which initiate the inflammatory cascade.

3. Allergy-associated contact urticaria: On skin mast cells, a particular IgE antibody attaches to allergens like latex gloves, eggs, and dog saliva. Contact urticaria, severe allergic reactions, and episodic acute or ordinary urticaria can result from this; however, chronic urticaria is not connected with allergies in adults. In rare situations, interactions with chemical molecules such as sorbic acid or benzoic acid can directly affect the vascular walls and produce urticaria, potentially by stimulating the production of PGD2.

4. Complement-associated urticaria: Angioedema caused by C1 esterase inhibitor deficiency is primarily triggered by the production of quinine as a result of complement activation, with bradykinin and histamine playing minor roles [7].

Non-immunologic urticaria

Mast cell and basophil degranulation can occur following exposure to some medicines such as codeine and other chemicals such as contrast agents used in radiology, with no IgE receptor activation necessary. The mechanism of urticaria formation or aggravation caused by aspirin, nonsteroidal anti-inflammatory medications (NSAIDs), and known allergens such as salicylates, azo dyes, and food preservatives remains unknown. However, leukotrienes and histamine release are most likely implicated. Angioedema produced by ACE inhibitors is thought to be caused by the inhibition of quinine breakdown [8].

Diagnosis and assessment

Urticaria is mostly diagnosed solely on clinical symptoms, with extra tests indicated only in exceptional situations and depending on clinical findings. In certain cases of acute urticaria, no laboratory tests are required. Furthermore, no laboratory tests are required in mild chronic urticaria. In the clinical history of urticaria, the elements listed in Table 3 should be considered. If an underlying allergy or urticarial vasculitis is suspected, the items in Table 4 and Table 5 should be evaluated.

Individual urticarial lesion duration can aid in the diagnosis of the following clinical patterns:

A) Urticarial lesions normally disappear within 2 to 24 hours of onset.
B) Contact urticaria: lesions might last up to 2 hours.
C) Delayed pressure urticaria: appears within 2 to 6 hours and dissipates within 48 hours.
D) Urticarial vasculitis: lesions are usually temporary.
E) Angioedema: if left untreated, it might last up to three days [3,9,10].

Diagnostic assessments

Table 6 summarizes the assessments used to diagnose urticaria. Recording the timing of urticaria

Table 3. Recommended items to consider during history-taking when evaluating a patient with urticaria

1. Time of onset of disease
2. Frequency/duration and provoking factors for wheals
3. Diurnal variation
4. Occurrence in relation to weekends, holidays, and foreign travel
5. Shape, size, and distribution of wheals
6. Associated angioedema
7. Associated subjective symptoms of lesions, for example itch, pain
8. Family and personal history regarding urticaria, atopy
9. Previous or current allergies, infections, internal diseases, or other possible causes
10. Psychosomatic and psychiatric diseases
11. Surgical implantations and events during surgery (for example, after local anesthesia)
12. Gastric/intestinal problems
13. Induction by physical agents or exercise
14. Use of drugs (e.g., non-steroidal anti-inflammatory drugs (NSAIDs), injections, immunizations, hormones, laxatives, suppositories, ear and eye drops, and alternative remedies)
15. Observed correlation to food
16. Relationship to the menstrual cycle
17. Smoking habits (especially use of perfumed tobacco products or cannabis)
18. Type of work
19. Hobbies
20. Stress (eustress and distress)
21. Quality of life related to urticaria; emotional impacts
22. Previous therapy and response to therapy
23. Previous diagnostic procedures/results

Table 4. Recommended history-taking questions when evaluating a patient with urticaria regarding an underlying allergy

• Does urticaria occur frequently only within 60 minutes (usually the first 20 minutes) after eating a particular type of food?
• Does urticaria occur only after taking a specific nutrient or physical exercise?
• Does urticaria occur after contact with latex?
• Does urticaria occur after exposure to specific allergens the patient is allergic to (e.g., cat, horse, grass, and contact with certain foods)?
• Does urticaria occur due to drugs that the patient receives (esp., aspirin/NSAIDs/ACE inhibitors)?

Table 5. Evaluating a patient with urticaria regarding urticarial vasculitis

• Does urticaria/angioedema look more severe than usual?
• Do lesions last for more than 24 hours?
• Are lesions painful or tender to touch rather than being itchy?
• Is there any evidence of subcutaneous bleeding, such as petechiae, purpura, or bruises?
• Is the patient suffering from underlying symptoms such as fever, fatigue, malaise, and arthralgia?

helps determine the cause of urticaria and keep track of when symptoms arise after exposure to triggers. The following tests may be relevant depending on the timing findings or the patient's medical history [4,10]:

1. Complete Blood Count (CBC): The test findings may help in determining the cause of urticaria. For example, parasite infections and medication responses cause an increase in eosinophils, whereas urticarial vasculitis causes an increase in neutrophils.

2. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR): A high ESR can indicate a persistent infection, vasculitis, or paraproteinemia. The CRP test can measure disease severity or therapy response [11,12].

3. Complete urine test: Urinalysis in cases of urinary tract infection as a cause of urticaria or renal involvement in urticarial vasculitis may reveal blood or protein.

4. Parasitology: Fresh stool tests or serological studies help identify parasitic infections in unexplained eosinophilia or in those with a history of travel to places where certain parasites are common.

5. Skin biopsy: A skin biopsy is required if urticarial lesions last longer than 24 hours or if physical examination reveals petechiae, purpura, or discomfort. A biopsy is also indicated if systemic signs such as fever, discomfort, or arthritis are noticed or if the lesions leave scars after healing.

6. Thyroid function tests and antithyroid autoantibodies: The likelihood of autoimmune urticaria arises when thyroid antibodies accompany chronic urticaria in children and adults. Thyroid function is normally normal in these people. However, monitoring is advised.

7. Serum complement: It is not necessary to study the C1 inhibitor if angioedema develops together with urticaria. A hereditary angioedema screening test is required in cases of angioedema without urticaria to measure C4 and C1 inhibitors (quantitative and functional). C4 and C3 should be tested in cases of urticarial vasculitis. Urticarial vasculitis combined with hypocomplementemia has a poor prognosis.

Complement measurement aids in the diagnosis of suspected cases of allergic urticaria or contact urticaria. If this test returns negative, an allergic reaction to foods or other allergens caused by IgE is unlikely.

Table 6. Diagnostic tests recommended in common types of urticaria

Type	Subtype	Common diagnostic tests (commonly recommended)	Supplementary diagnostic tests to identify underlying factors and rule out differential diagnoses
Spontaneous urticaria	Acute and episodic spontaneous urticaria	No tests recommended	No tests required
	Chronic spontaneous urticaria	Chronic spontaneous urticaria	Infectious diseases such as *Helicobacter pylori*, hypersensitivity type I (e.g., RAST), active autoantibodies, thyroid hormones and autoantibodies, skin tests including physical tests, pseudo-allergen free diet for 3 weeks, serum tryptase, ceasing medications (such as NSAIDs), autologous serum skin test, lesion biopsy
Physical urticaria	Cold urticaria	Cold challenge test with ice, cold water, and cold wind	CRP, CBC, ESR, cryoproteins; rule out other diseases, especially infections
	Delayed pressure urticaria	Pressure test (for 10-20 minutes)	No complementary tests required
	Heat urticaria	Heat challenge test and hot water	No complementary tests required
	Solar urticaria	Ultraviolet light and visible light with different wavelengths	Rule out other skin disorders caused by light
	Dermographic urticaria/ factitious urticaria	Dermographism test	CBC, ESR, CRP
	Aquagenic urticaria	Wearing wet clothing at body temperature for 20 minutes	No complementary tests required
	Cholinergic urticaria		No complementary tests required
	Contact urticaria	Prick/patch test	No complementary tests required

8. Autologous serum skin test: In this test, the patient's serum is injected intradermally. Urticaria and localized discoloration are signs of circulating autoantibodies against IgE receptors on the surface of mast cells. This approach is mostly used for research purposes and is not extensively adopted. The basophil histamine release assay, which is only accessible in a few sites, is the gold standard approach for detecting antibodies.

9. Cryoglobulins: Clotted samples taken at 37° C are sent to the lab. In secondary cold urticaria, the test may be positive.

10. Challenge tests: These tests are useful in determining the cause of physical urticaria and are briefly detailed below.

- **Cold urticaria:** For 20 minutes, a plastic bag containing ice is placed on the forearm. The skin is assessed when it has warmed up again.
- **Dermographism:** Light stroking is used to evaluate the skin. The test is considered positive if urticaria occurs within 10 minutes.
- **Aquagenic urticaria (caused by exposure to water):** The test is performed easily by submerging the body in 37 °C water for a few minutes or by laying a damp towel (the same temperature as the body) on the skin for a few minutes.
- **Cholinergic urticaria:** It is evaluated by exercise in a hot atmosphere.

Many patients with urticaria do not require any special laboratory tests. However, depending on the symptoms, additional testing may be required. Figure 1 illustrates the diagnostic techniques for urticaria and angioedema.

- **Diagnosis of urticaria in children:** The main concepts of urticaria diagnosis in children are identical to those in adults. Auto-inflammatory illnesses such as CAPS should be investigated in youngsters [4,13].

Treatment

In treating patients with urticaria, two approaches should be taken: identifying and removing the causes causing or exacerbating the condition (although this is not always attainable because urticaria is idiopathic in many cases) and treating urticaria symptoms.

A) Identification and removal of urticaria causes or aggravating factors

Identifying and removing the causes or aggravating factors is the first step in urticaria therapy. A high

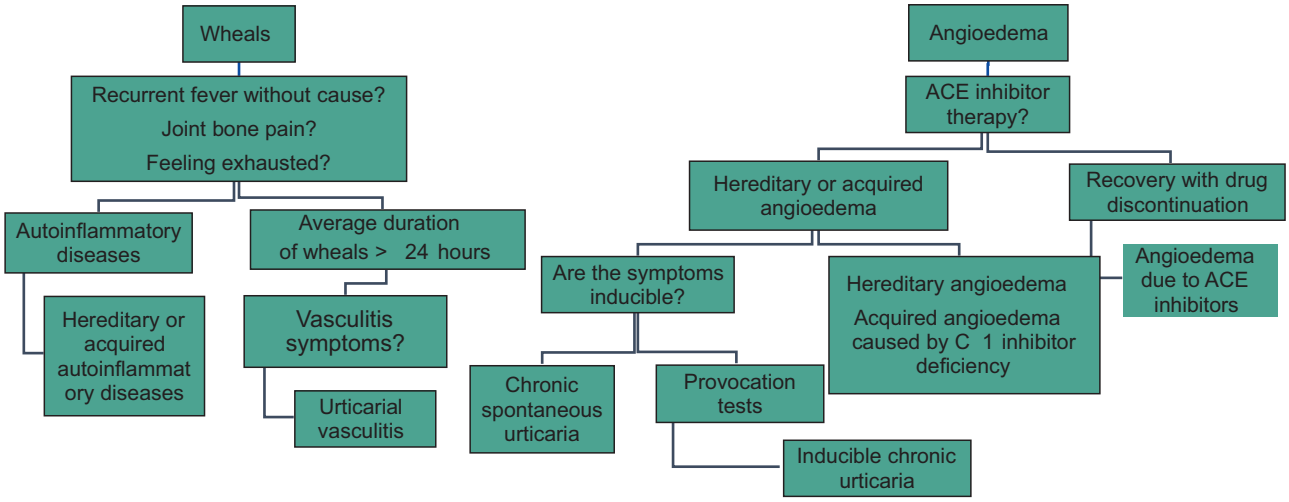

Figure 1. Diagnostic algorithm for approaching a patient with prolonged (> 6 weeks) wheals or angioedema [10]

number of urticaria sufferers have both chronic and physical urticaria. As a result, recognizing urticaria causes or exacerbating factors is critical in long-term treatment. Certain treatment options should be used in people with physical urticaria [13,14].

• **Infections and foods:** In some people with common acute and chronic urticaria, therapy of infection or inflammatory illnesses such as *Helicobacter pylori*-induced gastritis or avoidance of particular foods, additives, and medicines may be beneficial [15,16]. Analgesics can create new urticarial lesions and aggravate existing urticaria. Only a relapse following a double-blind provocation test can prove the role of these factors.

• **Stress**: In some cases of persistent urticarial itching, stress can trigger or increase itching. As a result, psychological counseling can benefit some patients [14].

• **Drugs:** Acute urticaria is frequently caused by medications. However, pharmaceuticals can also cause the development of chronic urticaria; suspicious drugs should be withdrawn and replaced with treatments from a different class. To the greatest extent possible, patients should avoid taking multiple medications and avoid unneeded therapies. Drugs that elicit IgE-independent reactions, such as aspirin, can cause new urticarial lesions and worsen existing ones. In 30% of chronic urticaria patients, aspirin can worsen the condition. Patients can, however, typically take low-dose aspirin for anticoagulant purposes. Aspirin and other NSAIDs are hence not indicated in people with persistent urticaria [15]. Angiotensin-converting enzyme inhibitors can cause angioedema but seldom cause persistent urticaria. Patients with chronic urticaria (with or without angioedema) are advised to avoid such medications. Other medicines aggravating chronic urticaria include opiates (codeine, morphine), oral contraceptives, and antidepressants (citalopram, statins, and alcohol) [17,18]. Avoid NSAIDs in patients whose urticaria increases with this class of medication. If NSAIDs are tolerated, and there are no therapeutic restrictions, use selective cyclooxygenase two inhibitors in chronic urticaria patients. However, when used as an antithrombotic medicine, little data supports the benefit of moving from low-dose aspirin to another antiplatelet drug.

• **Physical factors:** It is critical to precisely identify physical variables and their mechanical qualities in individuals with physical urticaria (Table 4). Many patients, however, have a very low threshold reaction to physical stimulation. As a result, it is not possible to completely control the disease [13,16]. Simple steps, such as utilizing bags with wide straps, could help prevent the development of symptoms in patients with delayed pressure urticaria or dermographism. In the therapy of cold urticaria, cold wind should be avoided. Knowing the specific wavelength of the sunshine is necessary to offer the patient proper sunscreen and light bulbs for treating solar urticaria.

• **Infections:** Urticaria can be caused or aggravated by a variety of infectious pathogens, including:

- Viruses
- Bacteria: dental root canal, sinus, gallbladder, and urinary tract infections, as well as *H. pylori*

- Fungi: nail fungal infections, tinea pedis, and candidiasis
- Parasites: strongyloidiasis, giardiasis, amoebiasis, and mites are examples of parasites. Intestinal worms usually induce eosinophilia. The absence of eosinophilia, however, does not rule out an infection [3,19].

• **Inflammatory processes:** Chronic urticaria can also be caused by chronic inflammatory disorders such as chronic gastritis, reflux esophagitis, or inflammation of the gallbladder or bile ducts. Independent of *H. pylori* infection, stomach ulcers are related to an elevated risk of chronic urticaria. This risk is greater in women aged 20 to 40 with stomach ulcers. As a result, stomach ulcers should be examined in patients with persistent urticaria and digestive symptoms [16].

• **Dysbiosis of the digestive tract:** Chronic urticaria causes changes in the population of numerous types of fecal bacteria. This modification can improve the permeability of the intestinal epithelium and the absorption of immune-stimulating substances. Probiotics may help with chronic urticaria control and can be a safe and efficient adjuvant in treating chronic urticaria. One trial found that adding probiotics to antihistamines did not boost effectiveness compared to antihistamines alone, but patients in the first group had a greater reduction in the degree of pruritus and the number of urticaria lesions [20].

• **Autoimmunity:** An active antibody exists against the alpha chain of the IgE receptor (FCRI) in certain patients with chronic urticaria. Anaphylactic reactions can occur due to factors that make receptors accessible to antibodies. Non-immune aggravating factors for urticaria can increase the number of accessible receptors directly or indirectly; thus, antibodies can cause urticaria [21].

• **Systemic diseases:** Chronic urticaria may be accompanied by hyperthyroidism or hypothyroidism (Hashimoto's thyroiditis). Levothyroxine medication may result in urticaria remission in some patients who do not have thyroid problems but do have autoantibodies [21].

• **Diet:** Patients suffering from chronic urticaria may benefit from avoiding pseudo-allergens. Extreme and needless diets, on the other hand, should be avoided unless absolutely required. It should be noted that pseudo-allergens typically worsen urticaria but do not cause it. Some chronic urticaria sufferers have pseudo-allergic reactions to food or food additives (such as artificial colors and preservatives). A vitamin should only be avoided if proven to induce urticaria. Most people with chronic urticaria do not benefit from allergic skin or blood tests. Pseudo-allergen/food additive-free diets should be followed for 3 to 6 months; symptoms typically subside in 50% of patients. It should be mentioned that avoiding specific foods with type I hypersensitivity (an uncommon urticaria-related allergy) improved urticaria within 24 to 48 hours. However, pseudo-allergen-free meals should be followed for 2 to 3 weeks before treating urticaria. Dietary limitations (allergens and/or pseudo-allergens) are only advised after a double-blind provocation test [13]. Vitamin D deficiency is more common in patients with chronic urticaria than in healthy controls, and vitamin D supplementation successfully reduces the intensity and duration of urticaria. Iron deficiency and low ferritin levels are also connected with chronic urticaria; iron deficiency treatment can be helpful in patients with chronic urticaria. Routine testing for vitamin D insufficiency is not advised [22].

• **Environmental factors:** Pollens, molds, sprays, animal dander, house dust mites, and smoke can all aggravate chronic urticaria. Urticaria might increase during pregnancy and before menstruation. Chronic urticaria has been linked to orthopedic implants, dentures, dental amalgams used in fillings, and intrauterine devices (IUDs). Stress, despair, and worry can all cause or exacerbate urticarial disease [23-26].

• **Contact urticaria:** Urticarial lesions are caused by contact with animals and certain materials, such as latex and some types of food, via an IgE-dependent process. Contact with the aforementioned drugs should be avoided in such patients to keep the sickness under control [23-26].

• **Hormonal changes:** Women are more likely than men to suffer from chronic urticaria. In certain women, the intensity of urticaria is determined by variations in sex hormones during the ovarian cycle. Urticaria worsens after menstruation and improves with oral contraceptive pills in many women. Significant improvement with GnRH analogs occurred in certain cases of premenstrual worsening of chronic urticaria with a positive skin prick test with progesterone [17,18].

B) Symptomatic treatment of urticaria

• **Antihistamines**: Antihistamines are mostly H1 receptor inverse agonists, which bind to the H1 receptor and block histamine binding to the H1 receptor. As a result, histamine activity is decreased. H2 receptor inhibitors are typically not included in the definition. Antihistamines of the first and second generations are known as sedating and non-sedating antihistamines, respectively.

First-generation antihistamines

Since the 1940s, first-generation antihistamines have been used to treat allergic rhinitis, allergic conjunctivitis, hives, cough, colds, and sleeplessness.

Because first-generation medicines are relatively lipophilic, they may cross the blood-brain barrier and cause drowsiness. They interact with alcohol and numerous medications, in addition to having hypnotic and anticholinergic properties. They also impact learning and brain performance by influencing the REM stage of sleep. As a result, they should not be used in adults or children for an extended period [4].

Due to the potentially dangerous adverse effects of first-generation antihistamines, their frequent use as the first line of treatment for chronic urticaria is not suggested, nor is it advisable to raise the dose. None of the first-generation antihistamines are more successful in treating urticaria than others in this class. After two hours, the maximal concentration of these medicines is reached [27].

Second-generation antihistamines

Second-generation antihistamines, like first-generation antihistamines, are inverse agonists of the H1 receptor. A low toxic-to-therapeutic dose ratio or broad therapeutic window distinguishes this class of medications. As a result, it is possible to use these medications in excess of the indicated amount to treat chronic urticaria.

This class of medications is less lipophilic and produces less drowsiness. They are also very selective and have fewer anticholinergic effects than the first group. Available on the market are fexofenadine, loratadine, cetirizine, and desloratadine. Levocetirizine was previously available on the market. Terfenadine and astemizole have been taken off the market due to cardiovascular problems, such as a prolonged QT interval.

Most second-generation antihistamines have been studied in chronic urticaria, and there is enough evidence to support their usage. It is also recommended to raise the dose up to four times if needed (off-label), depending on patient tolerance and the absence of contraindications (the existing clinical evidence for desloratadine and levocetirizine is stronger in this regard). The exception is mizolastine, as increasing the dose of this agent is not suggested due to cardiotoxicity and electrolyte imbalances. Dose augmentation is linked to an increase in the effectiveness of the drug in managing pruritus but also heightens the chance of sleepiness. As a result, the patient should be notified whenever the dose is increased.

As the first line of treatment for chronic spontaneous urticaria, a second-generation antihistamine at a standard dose is recommended to be used regularly (not just in cases of pruritus or other troubling symptoms), and if there is no response, the dose should be increased (no more than four times). There is no difference between second-generation antihistamines, and using multiple second-generation antihistamines simultaneously is not advised [4].

Table 7 and Table 8 show the generic name, brand

Table 7. Generic name, brand name, dosage form and recommended dose for adults of second-generation H1 receptor inhibitor antihistamines

Generic name	Brand name (Manufacturer's name)	Drug availability under generic name	Dosage form	Recommended dose in adults
Bilastine	FAESA pharma (Spain)	No	20 mg tablet	20 mg once a day
Cetirizine	Zyrtec (Pfizer)	Yes	5 and 10 mg tablets, 5 mg/ml syrup	10 mg once a day
Desloratadine	Clarinex (Merck)	Yes	5 mg tablet, 0.5 mg/5 ml syrup	5 mg once a day
Fexofenadine	Telfast (Sanofi)	Yes	60, 120 and 180 mg tablets	180 mg once a day or 60 mg twice a day
Levocetirizine	Xyzal (Sanofi)	Yes	5 mg tablet	5 mg once a day
Loratadine	Claritin (Schering)	Yes	10 mg tablet, 5 mg/ ml syrup	10 mg once a day
Rupatadine	RupalUriach (Spain)	No	10 and 200 mg tablets	10 or 20 mg once a day

Table 8. Pharmacokinetic characteristics of second-generation H1 receptor inhibitor antihistamines in Iran

Name	Time to maximum serum level (hours)	Bioavailability (%)	Binding to protein (%)	Half-life (hours)	Active metabolite	Excretion
Cetirizine	0.5–1.5	70	93	8.3	Levocetirizine	More than 70% through urine
Desloratadine	3	100	82–87	27	Desloratadine	Negligible urinary excretion
Fexofenadine	1–3	85	60–70	14.4	Terfenadine premedication	80% in the feces
Levocetirizine	0.75	77	90	11	Cetirizine active metabolite	Negligible urinary excretion
Loratadine	0.7–1.3	-	97.1	2–4	Desloratadine	Negligible urinary excretion

name, formulation and dosage, pharmacokinetic characteristics, and recommended dosage of second-generation H1 receptor inhibitor antihistamines in Iran for adults.

Desloratadine

This medication is the active metabolite of loratadine, which is swiftly absorbed from the digestive tract and has a half-life of up to 24 hours. It is a non-hypnotic, highly specific antagonist of peripheral H1 receptors. This medication has 15-150 times the binding strength to the H1 receptor in vivo and is more efficacious than loratadine. Six hours after delivery, 63% of desloratadine is still linked to the H1 receptor, causing the drug's impact to last longer. A higher dose is required for a successful response in chronic urticaria with ESR > 20 or high anti-thyroid antibody levels. Desloratadine has no anticholinergic side effects and has been established in numerous human and animal tests to be safe regarding cardiovascular side effects. Desloratadine does not affect driving or other occupations that need attentiveness, and it improves people's quality of life. The safety of this treatment has been established in youngsters and the elderly, and there is no need to change the drug dose in these patients. Desloratadine does not cause drowsiness, and this effect is not noticed even when doses larger than the prescribed drug dose (up to four times) are used. This medication has no food interactions [28-30].

Table 9. The mechanisms of action of omalizumab in treating chronic urticaria

1- Decreasing the free levels of IgE and IgE receptors
2- Reducing the release of inflammatory substances from mast cells
3- Increasing the number of basophils and improving the function of IgE receptors
4- Decreasing the activity of autoantibodies against IgE and FcεRI
5- Reducing the activity and function of abnormal IgEs
6- Reducing binding and activity of IgE autoantibodies against autoantigens
7- Preventing the release of various inflammatory mediators
8- Reducing the effect of coagulation system activity on the development of hives

Cetirizine

Cetirizine is hydroxyzine's carboxylic acid metabolite. A single dose of 10 mg taken orally can relieve urticaria symptoms for up to 24 hours. At the indicated dose, anticholinergic symptoms would be limited. Researchers noted that 13.7% of patients suffered drowsiness after taking the recommended dose, while 6.3% of patients taking a placebo also reported drowsiness. This problem becomes more common as the dose is increased. It is recommended that people with chronic renal or liver disorders reduce their intake to 5 mg. Cetirizine can be used to treat chronic urticaria. Significant medication interactions and side effects (including cardiotoxicity) are yet to be reported [31-33].

Fexofenadine

Like other second-generation antihistamines, fexofenadine is a selective H1 receptor inverse agonist whose adverse effects are similar to placebos. Even though it is generated from terfenadine, it has no hepatic metabolism and is eliminated almost completely. Fexofenadine has no anticholinergic effects, and multiple human and animal investigations have shown that it has a benign cardiovascular profile. Fexofenadine does not affect driving or other occupations requiring attentiveness, improving the patient's quality of life. This medicine is safe in children, older adults, and patients with liver failure or renal illness; the dose does not need to be modified in these individuals. Fexofenadine does not produce drowsiness, even at greater than advised doses. There is no report of drug resistance. Fexofenadine is rapidly absorbed after oral administration and acts

much faster than loratadine. The medicine achieves its maximal blood concentration in 1 to 3 hours, and its effects extend for up to 24 hours. Scientific data suggests that taking 180 mg once daily is useful for treating chronic urticaria. There have been no reports of clinically significant medication interactions as of yet. Fexofenadine effectively absorbs vitamin C, which lowers its absorption by roughly 30% [31-34,35].

Loratadine

Loratadine is a piperidine-based antihistamine of the second generation. Loratadine's anticholinergic effects, drowsiness, and other adverse effects are modest at the recommended dose. Desloratadine is the active metabolite of this medication. The medication has an 8 to 11-hour half-life. Although liver or kidney dysfunction does not affect the drug's pharmacokinetics, drug dose adjustment is required for individuals with chronic liver or kidney problems. A single oral dose of 10 mg often suppresses urticaria symptoms for 12 hours. The medicine has not been found to be ineffective. Despite its effect on potassium channels, loratadine does not produce cardiac arrhythmia. No interactions between this medication and treatments that alter cytochrome P450 3A4 (CyP3A4) are known. Loratadine is primarily used to treat chronic urticaria [36-38].

Levocetirizine

Cetirizine's R-enantiomer and main metabolite is levocetirizine. It appears to be more effective in reducing urticaria than loratadine. It causes minor drowsiness and anticholinergic effects. It is suggested to treat urticaria in people above six years old, with a daily dose of 5 mg [30,38].

H2 receptor antagonists

There is little evidence to advocate routine use or the addition of H2 antihistamines to H1 second-generation antihistamines in people with chronic urticaria, but they may be useful in some cases with dyspepsia. Famotidine is preferred over cimetidine since it has fewer negative effects and medication interactions [39].

Steroids

Systemic steroids are only indicated for treating acute attacks at a maximum dose of half a milligram per kilogram of body weight for a maximum of 10 days. Furthermore, there is no need to taper the medication [39].

Treatment of special cases

Children

Urticaria affects 1% of children, with equal numbers of men and females affected. Overall, 78% of cases are chronic urticaria, while 22% are physical urticaria. H1-antihistamines of the first generation have greater problems and a lower safety profile than the second generation; hence, they are not recommended as the first line of treatment in children with urticaria. Many nations forbid the use of second-generation H1 antihistamines in children under the age of six months. Bilastine, desloratadine, cetirizine, rupatadine, fexofenadine, loratadine, and levocetirizine are all effective and safe in children. When selecting these antihistamines for children, the age and availability of the drug should be considered, as not all of them are accessible as syrups or quick-dissolving tablets [40]. Various countries have various minimum ages. Because increasing the dosage of antihistamines and other treatment strategies in children has not been thoroughly explored and evaluated, all further therapy steps should be considered individually and carefully in each patient. In addition, the algorithm recommends short-term usage of corticosteroids 0.5-1 mg/kg for five days, which should be used only in rare circumstances in children [11,40].

More research is needed to evaluate the disease's natural course, the benefit-loss ratio, the beneficial effects of existing medicines, and the use of biologics in treating chronic urticaria in children [41].

Considerations

1- If the child's overall health is poor or they have elevated inflammatory markers, they should be referred to a rheumatologist or an auto-inflammatory disease expert.
2- If the child tests positive for a parasite infection, it should be treated. Eosinophilia, gastrointestinal symptoms, and recent travel to other countries are all signs of parasite infection.
3- Cetirizine, levocetirizine, loratadine, and rupatadine are H1 antihistamines that can be taken in children as young as two years old if necessary. Desloratadine is permitted from the age of six months, and

chlorpheniramine from the age of one year.
4- Montelukast's side effects, including dysphemia, are more severe in children than in adults.
5- Omalizumab is not approved for children in England, but it has been used successfully in children under the age of 12 with chronic urticaria and inducible urticaria at a dose of less than 150 mg every four weeks, up to the age of six, and in a few cases at earlier ages [42].
6- Cyclosporine is used off-label with a 3-4 mg/kg dose.
7- There is limited evidence to support the use of phototherapy in children or during pregnancy.
8- Cold and cholinergic urticaria were the most common types of induced urticaria in a cohort study of 64 children with chronic urticaria (CINDU) with an average age of 12.5 years. In general, this type of urticaria is uncommon in children and is related to increased CD63 levels and thyroid issues [43].

Pregnancy and lactation

Treating urticaria in all pregnant women is unnecessary, but it may impact their quality of life. Due to the lack of drowsiness, second-generation antihistamines are the first line of treatment. Cetirizine and loratadine are safe to take throughout pregnancy and nursing. To control urticaria, a dose increase every two weeks may be required, up to a maximum of four times the normal dose.

First-generation antihistamines are not recommended during pregnancy or lactation since they pass into the breast milk.

In the case of severe urticaria, oral corticosteroids may be prescribed for three days but should not be continued beyond that during pregnancy.

A cohort trial revealed no evidence of an increased risk of congenital abnormalities with omalizumab in pregnant women with urticaria compared to a control group [43-45].

Use of other drugs in chronic urticaria

Omalizumab

Omalizumab is a humanized IgG1 monoclonal antibody that selectively blocks IgE molecules from attaching to mast cells and basophil IgE receptors. It is a safe and effective therapy method for patients with chronic spontaneous urticaria (CSU) resistant to antihistamines [46,47]. It has been used in the United States and Europe since 2014 to treat CSU in patients over 12 who are refractory to standard therapy [47].

Because of the increased half-life of the drug and IgE complex, as well as the difficulty in distinguishing IgE and the type of complex when measuring the IgE level, the usage of omalizumab can increase the amount of total IgE (as opposed to the level of free IgE) by 2 to 11 times (Table 9) [48,49]. The advantages of omalizumab treatment can be noticed in some patients as early as the first week, although patients must be warned that improvement in their symptoms may not be visible right away [48]. Typically, the best therapy impact and reduction in disease symptoms appear three months after treatment begins; however, this effect can sometimes be delayed for up to six months. Typically, no increase in treatment effectiveness is noted after six months. As a result, if a suitable therapeutic response is not seen after six months of commencing the medicine, it is preferable to move on to the next line of treatment [49].

A high serum IgE level, associated with a quick response to therapy, is the most critical data that can demonstrate the drug's efficacy before treatment begins. However, if a significant level of IgE is not detected, this response to treatmentmay be observed longer after therapy begins.

Omalizumab is administered for chronic urticaria at 150 or 300 mg subcutaneous injections every 2 or 4 weeks, regardless of the patient's weight or serum IgE level. The licensed dose and duration of treatment vary by country, but research shows that the 300 mg dose has the most efficacy, and the chances of a response increase with at least three injections every four weeks. However, in patients who have a return of symptoms sooner than four weeks between medications, 150 mg dosages every two weeks can be utilized [50-52]. Doctors withhold the treatment after six months; if the condition recurs, they restart treatment for another six months [53,54].

Omalizumab has also been proven to be effective in treating various types of physical-mechanical urticaria, such as cholinergic urticaria, cold urticaria, solar urticaria, heat urticaria, dermo graphic/induced urticaria, and delayed pressure urticaria. Patients who relapse after discontinuing treatment may benefit from omalizumab retreatment [55-58].

Omalizumab is regarded as a safe medication. In clinical studies, the incidence and severity of

unpleasant and serious adverse events were minimal and comparable to the placebo group. Although there were initial worries regarding a heightened risk of malignancy, current data suggest no links between omalizumab and malignancies [59].

Omalizumab may increase nematode parasite infections, although it does not affect the severity of the disease or its response to treatment. Checking for nematodes and *Strongyloides stercoralis* is therefore advised prior to commencing omalizumab [59-63].

There is no need to discontinue omalizumab if you have a skin infection, a non-skin infection, a viral or fungal infection, or a vaccine. It is preferable to wait seven days between immunization and omalizumab to distinguish potential side effects caused by each medication from the other [64].

There is no evidence of a significant rise in upper respiratory infections in patients with chronic urticaria who have received omalizumab; thus, in the absence of evidence, it is preferable to make a decision based on the patient's clinical conditions [65,66].

Among the reported side events is the possibility of anaphylaxis, which might occur in 0.1–0.2% of individuals [67]. A high proportion of patients who developed an anaphylactic shock due to omalizumab had previously experienced a non-omalizumab-related shock, and the underlying cause is unknown. The risk of anaphylaxis increases during the first three injections and reduces as the treatment progresses; therefore, around 40% of instances of anaphylactic shock occur during the first three injections. Around 30% occur between the fourth and twentieth injections, with the remainder occurring after the 20th injection [68,69].

A skilled individual administers omalizumab in a place with adequate facilities and must be able to manage the patient if anaphylactic symptoms arise. After the injection, the patient should be followed for at least 30 minutes. Following that, the medication injection can be performed for the fourth time at home, with the patient receiving the requisite shock management training [70,71].

Prior to giving this medication to patients with chronic urticaria, no blood tests are required to assess dosage or injection times [72]. Omalizumab is a pregnancy category B medicine that can be used safely in pregnant patients, and there have been no reports of teratogenicity [73,74].

Ligelizumab

Ligelizumab is an anti-IgE monoclonal antibody that binds 50 times more to IgE than omalizumab and offers a better percentage of improvement with longer efficacy than omalizumab, according to phase 2 research [75,76].

Dupilumab has recently been found in clinical trials to be useful in treating chronic urticaria in adults. Mepolizumab and reslizumab have also been linked to successful chronic urticaria treatment. Clinical trials are now being conducted to determine their efficacy in patients with chronic urticaria [77].

Immunosuppressive drugs

Immunosuppressive medications are frequently employed in treating chronic urticaria; however, they have various therapeutic effects and qualities.

Methotrexate (MTX)

Methotrexate (MTX) has immunomodulatory and anti-inflammatory properties, and it may lower functional autoantibodies, which are found in 30% of individuals with spontaneous chronic urticaria. Although MTX is sometimes used as a third-line treatment for chronic urticaria, a meta-analysis found that combining MTX with antihistamines did not improve treatment-resistant urticaria management. It should be emphasized that this review only included two randomized trials [78].

In a retrospective study of ten chronic urticaria patients who were resistant to antihistamines and omalizumab, adding MTX at a dose of 15 mg per week as a subcutaneous injection over a 5.1 ± 2.4-month period improved the development or good control of chronic urticaria in 70% of patients and improved relative response in 10% of patients. The medicine was well tolerated by 80% of the patients. Finally, it appears that MTX, alone or in combination with other medications, is beneficial in people resistant to omalizumab and antihistamines [79].

In the studies, the MTX dosage ranged from 5 to 25 mg per week. Since MTX has a considerably better safety profile than cyclosporine, it may be a viable alternative for patients resistant to the combined treatment of omalizumab and antihistamines [78].

Cyclosporine

Cyclosporine is the second alternative drug

in individuals with persistent urticaria that is resistant to treatment. Cyclosporin A (CSA) is an immunosuppressive medication that limits T helper cell activation by decreasing the synthesis of inflammatory cytokines. The binding of CSA and cyclophilin inhibits the activity of calcium-urine phosphatase and reduces the translation of the cytokine genes TNF, L-4, L-3, and L-2, as well as the release of histamine, leukotriene, and prostaglandin by mast cells and basophils, and serum levels of 1L-2R, 1L-5, and TNFα.

Cyclosporine is the most effective alternative medicine verified in placebo-controlled randomized trials in 15–20% of antihistamine-resistant chronic urticaria patients who do not respond to omalizumab.

In adults, the response rate to a common dose of 4 mg/kg/day of cyclosporine is 60–70%; however, some studies put this figure at 26–33%. A meta-analysis found that at weeks 4, 8, and 12, the response rate was 54%, 66%, and 73%, respectively [80].

A UK retrospective analysis found that an omalizumab-treated cohort outperformed a cyclosporine-treated cohort regarding physician's opinion, DLQI, symptoms, and quality of life [80].

Cyclosporine is more effective in patients with positive basophil activity tests (BAT) and basophil histamine release assessments (BHRA). A shorter duration of urticaria and a greater initial intensity of urticaria also indicate a favorable response to cyclosporine treatment, but a reliable laboratory biomarker to predict a positive reaction to this medication is currently lacking [80].

Cyclosporine can cause side effects such as high blood pressure, kidney toxicity, headache, nausea, abdominal discomfort, and infections; hence, monitoring blood pressure, kidney function, and cyclosporine levels every six weeks is essential.

Leukotriene receptor antagonists

Montelukast and zafirlukast are medications that can be used to treat persistent spontaneous urticaria. Montelukast is backed by more research and is more routinely utilized. It has a tolerance and side effect profile that is acceptable. Because the utility of their effects is debatable, monotherapy with these medications is not advised. Their combination with antihistamines is more effective than antihistamines alone [11,40,81].

Anticoagulant and antifibrinolytic factors

Some studies have suggested that inflammation and coagulation activation play a role in the etiology of chronic spontaneous urticaria (CSU). Although the specific mechanism of the coagulation cascade in CSU is unknown, certain case reports and research have suggested that anticoagulant and antifibrinolytic medicines may have a role. Heparin, oral anticoagulants, and tranexamic acid are among the medications utilized. Because the research outcomes differed and the sample sizes were generally small, the exact urticaria-related roles of the coagulation pathway and the medications utilized remain unknown [78].

Antidepressants

Antidepressant medications have shown anti-inflammatory and immunomodulatory effects in animal models. Doxepin is a tricyclic antidepressant with significant antagonistic effects on H1 and H2 receptors; the best results are usually seen within a few days. Fifty individuals with CSU were evaluated to compare responses to doxepin (10 mg three times a day) and diphenhydramine (25 mg three times a day) treatment. Pruritus and hives were completely or partially controlled in 74% of doxepin patients but just 10% of diphenhydramine patients. Furthermore, doxepin had weaker hypnotic effects than diphenhydramine [82].

Antidepressants' significance in patients with persistent spontaneous urticaria who do not have psychiatric issues is uncertain, and larger clinical studies are needed to gather additional information.

Other anti-inflammatory or immunosuppressive factors

Dapsone

Dapsone is an antibacterial sulfone that may alleviate the symptoms of persistent spontaneous urticaria. It works by interfering with the release or activity of neutrophil lysosomal enzymes, limiting their migration and adherence, and purifying oxygen-free radical mediators.

Dapsone was effective in CSU and chronic autoimmune disease in placebo-controlled studies and a retrospective evaluation, with a mean time to improvement of 1.1 months and a complete response time of 5.2 months. However, further evidence is required [78,83,84].

Sulfasalazine

Sulfasalazine is an anti-inflammatory derivative of 5-aminosalicylic acid (5-ASA) that reduces leukotriene and prostaglandin synthesis, alters adenosine release, affects neutrophils, inhibits degranulation of mast cells by TGF, and affects B lymphocytes. This medication is effective in treating CSU. In a retrospective study of 39 patients with chronic urticaria resistant to treatment in the first three months, the addition of sulfasalazine resulted in symptomatic improvement in 84% of patients and complete improvement in 52% in the first six months and complete improvement in symptoms after discontinuation of the drug in 35%. Side effects include headache, nausea, increased liver enzymes, leukopenia, and rhabdomyolysis. In one case report, a combination of mycophenolate mofetil and sulfasalazine effectively managed chronic urticaria that had become resistant to sulfasalazine alone [85].

Hydroxychloroquine

In 2020, a systematic evaluation of 7 studies and 211 patients found moderate-quality evidence of hydroxychloroquine's positive benefits on urticaria symptoms. A case report and a case series both confirmed that hydroxychloroquine provided a good treatment response. Nonetheless, there is limited evidence that this medicine helps to resolve urticaria, and multicenter placebo-controlled studies are needed [86].

Other treatments and medications

1) H2 antagonists
2) Interferon
3) Plasmapheresis
4) Phototherapy
5) IVIG/IGTV
6) Mycophenolate mofetil
7) Oral tacrolimus

There is little evidence of the beneficial effects of these alternative treatments in urticaria, but they may be useful in some patients with specific clinical conditions.

Phototherapy (NBUVB, UVA, and PUVA for 1–3 months) may help in chronic urticaria and dermographism alongside antihistamines, but the problem of carcinogenesis is considered [42].

Treatments that should not be prescribed (have been ineffective in randomized clinical trials):

- Tranexamic acid and sodium cromoglycate in chronic spontaneous urticaria
- Nifedipine in symptomatic dermographism or factitial urticaria
- Colchicine and indomethacin in delayed pressure urticaria [42].

There is inadequate evidence to recommend the following treatments and interventions:

- Colchicine
- Cyclophosphamide
- Dipyridamole
- Interleukin 1 (IL-1) antagonists such as anakinra
- Psychological interventions
- Pyrocin
- TNF antagonists
- Warfarin [42]

Vitamin D and chronic urticaria

Several studies have linked vitamin D deficiency with allergic illnesses such as allergic asthma, allergic rhinosinusitis, atopic eczema, and food allergies. According to certain research, people with persistent spontaneous urticaria have lower serum vitamin D levels than controls. According to a 2018 systematic study, the prevalence of vitamin D deficiency is higher in people with CSU. The mechanisms are unknown and are yet to be demonstrated. It has been proposed that patients with low serum vitamin D levels and chronic urticaria have a greater probability of recovery if vitamin D supplements are administered. For patients with refractory CSU and low serum vitamin D levels, high-dose vitamin D can be used as an additional therapy for 4–12 weeks. However, further research is needed to determine the final dose and cut-off levels of vitamin D supplementation [80].

Treatment algorithm

Considering the available evidence, the algorithm presented in figure 2 is suggested for the treatment of urticaria.

Prediction of chronic urticaria period and response to treatment

Clinical features and laboratory indicators influence the course of the disease, its activity, and the responsiveness to treatment in chronic urticaria. Although none are 100% effective, they can assist patients in understanding the severity and potential

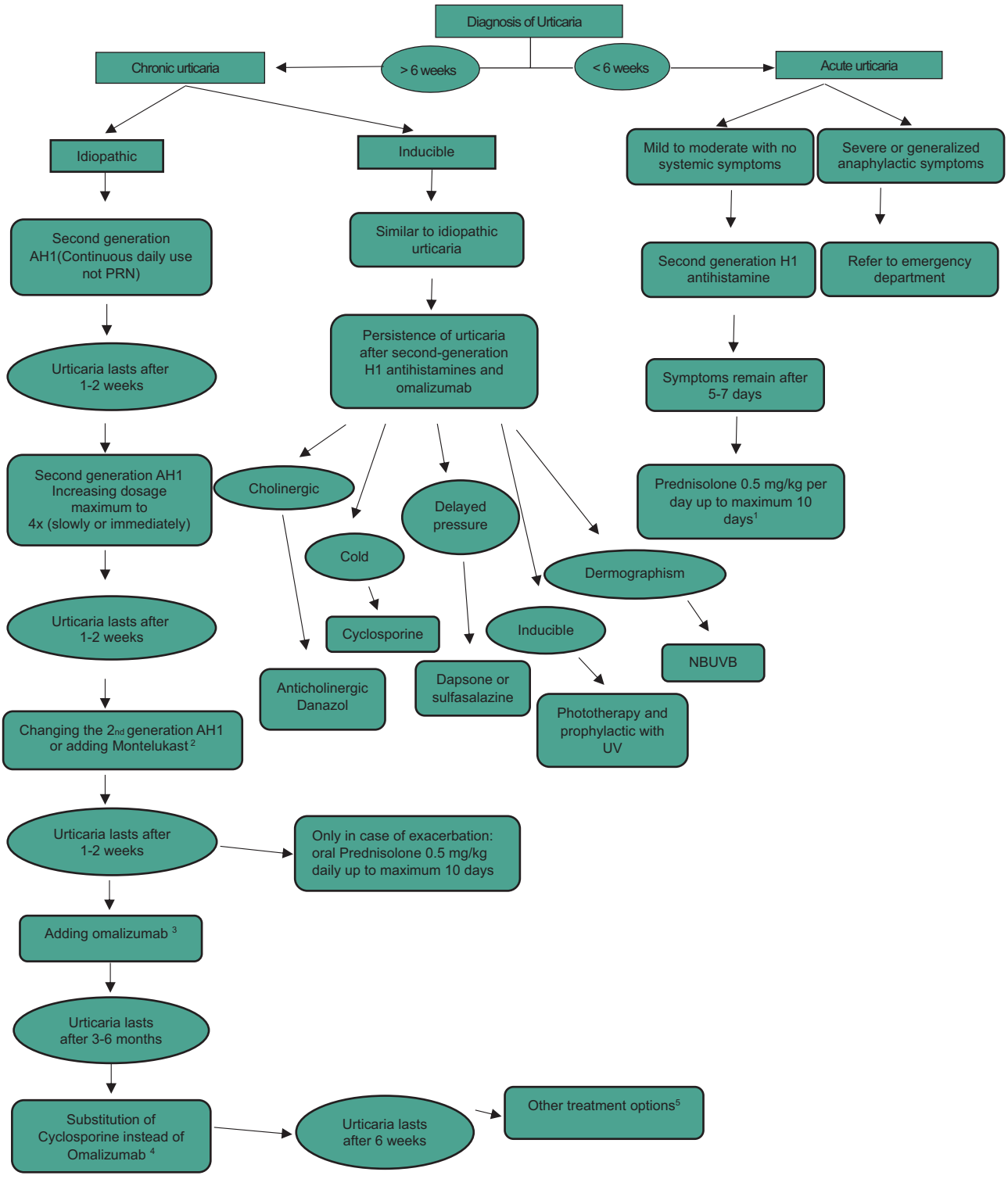

Figure 2. Algorithm of urticaria treatment

- It can be stopped at once, there is no need to gradually reduce the dose.
- Including: Adding 1st generation AH1, H2 antihistamine (In case of gastrointestinal symptoms), Doxepin
- Subcutaneous injection 300 mg every 4 weeks, if there is no response, the dose can be increased to 600 mg every 4 weeks or 300 mg every 2 weeks.
- 3-5 mg/kg daily for a maximum of 3-6 months.
- Other treatments (Azathioprine, Dapsone, Hydroxychloroquine, Methotrexate, Mycophenolate mofetil, IVIG, NBUVB, Sulfasalazine, Tacrolimus, and Tranexamic acid (Angioedema without Urticaria).

length of their illness and treatment expectations. Chronic inducible urticaria, high disease severity, high CRP, or angioedema, for example, imply prolonged CSU with a poor response to antihistamine treatment [11].

In acceptable doses, H1 antihistamines help about 45% of patients with persistent spontaneous urticaria. Increased doses work for the remaining 2.3%.

Omalizumab responds to 2.3% of unfavorable responses to H1 antihistamines, and a similar percentage overlap with cyclosporine and respond effectively to treatment. However, there is little evidence for cyclosporine, with responses ranging from partial to complete. As a result, in many cases of CSU, these medications alone are insufficient to suppress the disease totally.

Approximately 50% of persons with CSU recover fully after 6 months to 5 years (perhaps longer if angioedema is present), 20% have active disease after 10 years, and 10% have active disease after 20 years. This prolonged course most likely applies to persons with severe inducible urticaria, with fewer therapeutic options and information [42].

Treatment response assessment

It is preferable to use a measurement instrument to assess the severity of the disease and the response to therapy based on the duration of the condition and how it evolves over time. The Dermatology Life Quality Index (DLQI) and Urticaria Activity Score over 7 Days (UAS7) are the most commonly used instruments for treatment response assessment (Appendix 1) [87].

Authors contributions

All authors have been involved in the selection of papers, development of the guideline, manuscript preparation and approval.

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Appendix 1. Quality of Life Index in Skin Diseases [88]

Name:		Surname:	
Diagnosis:			
Date:	Year:	Month:	Day:
Hospital No:			
Score:			
Address:			

The purpose of this questionnaire is to measure how much your skin disease has affected your life during the past week. Please an "X" mark in the box of your answer

1) During the last week, to what extent has your skin been itchy, uncomfortable, painful, or burning?
☐ Extremely ☐ Very ☐ Moderately ☐ Slightly ☐ Not at all
2) During the last week, how often have you been embarrassed or nervous because of your skin disease?
☐ Extremely ☐ Very ☐ Moderately ☐ Slightly ☐ Not at all
3) During the last week, to what extent has your skin disease prevented you from going shopping or doing housework?
☐ Extremely ☐ Very ☐ Moderately ☐ Slightly ☐ Not at all
4) During the last week, to what extent has your skin disease affected the type of clothes you wear?
☐ Extremely ☐ Very ☐ Moderately ☐ Slightly ☐ Not at all
5) During the last week, to what extent has your skin disease affected your social or recreational activities?
☐ Extremely ☐ Very ☐ Moderately ☐ Slightly ☐ Not at all
6) During the last week, to what extent did your skin disease make it difficult for you to exercise?
☐ Extremely ☐ Very ☐ Moderately ☐ Slightly ☐ Not at all
7) During the last week, has your skin disease prevented you from working or studying?
☐ Yes ☐ No
If the answer to the previous question is "yes", during the past week, to what extent has your skin obstructed you to work or study?
☐ Extremely ☐ Very ☐ Moderately ☐ Slightly ☐ Not at all
8 (During the last week, to what extent has your skin disease caused problems in your relationship with your spouse, close friends, or relatives?
☐ Extremely ☐ Very ☐ Moderately ☐ Slightly ☐ Not at all
9) During the last week, to what extent has your skin disease caused problems in your sexual relationship with your partner?
☐ Extremely ☐ Very ☐ Moderately ☐ Slightly ☐ Not at all
10) During the last week, how many of your daily problems, such as making your home messy or dirty or wasting your time, were related to treating your skin?
☐ Extremely ☐ Very ☐ Moderately ☐ Slightly ☐ Not at all

Fill out the following questionnaire within 7 consecutive days. Your answer will help your doctor determine how severe your chronic urticaria is. Please evaluate the "number of urticaria " and "severity of pruritus " scores daily. Please bring the filled questionnaire with you for your next visit.

Date	**Extremity of urticaria per day**				**+**	**The amount of pruritus per day**				**=**	**The total sum of the daily evaluation of urticaria**						
First Day	0	1	2	3		0	1	2	3		0	1	2	3	4	5	6
Second Day	0	1	2	3		0	1	2	3		0	1	2	3	4	5	6
Third Day	2	1	2	3		0	1	2	3		0	1	2	3	4	5	6
Fourth Day	0	1	2	3	+	0	1	2	3	=	0	1	2	3	4	5	6
Fifth Day	0	1	2	3		0	1	2	3		0	1	2	3	4	5	6
Sixth Day	0	1	2	3		0	1	2	3		0	1	2	3	4	5	6
Seventh Day	0	1	2	3		0	1	2	3		0	1	2	3	4	5	6

Evaluation number of urticaria within seven days:

Evaluation urticaria within seven days:

Evaluation of urticaria activity (UAS7)		
Score	**Urticaria**	**pruritus**
0	Nonexistence	Nonexistence
1	Slightly (less than 20 inflammations in 24 hours)	Slightly (It is there but not annoying)
2	Moderately (20 to 50 inflammations in 24 hours)	Moderately (It is annoying but does not interfere with daily activities)
3	Extremely (more than 50 inflammations in 24 hours or large areas covered by inflammation)	Extremely (Extreme pruritus that is quite annoying and causes problems for sleep and daily activities)

marked improvement of renal function and reduction of proteinuria after therapy with human anti-interleukin-1β monoclonal antibody canakinumab. Clin Rheumatol. 2015;34(7):1311-6.

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