Management of urticaria: update of Iranian Society of Dermatology clinical practice guideline

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Important notice: All authors are shared first author.

Received: 12 August 2018
Accepted: 14 September 2018

Urticaria is a common and challenging skin disorder. Diagnosis and treatment of urticaria is not limited to the field of dermatology. General physicians, allergologists and clinical immunologists are also commonly involved in the management of patients with urticaria.

Iranian Society of Dermatology developed a clinical practice guideline concerning diagnosis and treatment of urticaria that was published in 2015. The current guideline is an update to the previous one and includes findings related to this subject which has been published in the medical literature from 2015 to August 2018.

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

Iran J Dermatol 2018; 21: 105-123

INTRODUCTION

Urticaria is a common and challenging skin disorder. The prevalence rate of urticaria is 1% to 5% in the general population. Management of urticaria is not limited to dermatologists. General physicians as well as allergologists and clinical immunologists are commonly involved in the

management of patients with urticaria.

One of the missions of the Iranian Society of Dermatology is to develop strategies to provide the best possible management for patients suffering from dermatological conditions. To accomplish this mission, the Society assigned a committee to search and critically appraise the recent research evidence and available guidelines in order to develop a clinical practice guideline concerning diagnosis and treatment of urticaria.1,2 As it was mentioned in this guideline and in light of new evidence becoming available in the past 3 years, it was necessary to update the guideline.

Methodology of Updating

In order to update the guideline, the following activities were carried out:

1. Identification of the topic: The incidence rate of urticaria is high and the disease causes serious problems for the patients. Keeping the physicians' knowledge up-to-date about new diagnostic techniques and treatments of urticaria based on the availability of such techniques and therapies in Iran may improve the services provided for patients with urticaria. Therefore, "urticaria" with an emphasis on spontaneous and chronic types of the disease was selected.

2. Target audience: Dermatologists practicing medicine in Iran were considered to be the major target audience for this clinical practice guideline.

3. Agenda: To update the practical clinical guideline on the management of urticaria, an expert panel was formed by the members of the Iranian Society of Dermatology. The panel included faculty members of the departments of dermatology and skin diseases' research centers. The panel was responsible for scheduling the meeting sessions and conducting the activities required for the development of the guideline.

4. Systematic review of the relevant medical literature: The first step was to search "PubMed" electronic database using "urticaria", "guideline", "systematic review" and "clinical trial" as keywords and "title/abstract" as the search filter from the beginning of 2015 until the end of August 2018. Among 159 retrieved titles and abstracts, 47 manuscripts were selected and used for the update of the guideline

5. Guideline development: The Guideline Development Committee was provided with the resources to oversee the progress of the clinical practice guideline development. All the Committee members commented on the guideline sections presented and the feedback was provided to the member responsible for each section.

6. Accreditation: The updated guideline was sent to the members of the Dermatology Board Certificate Examination and the chairs of the departments of dermatology in Iran and then it was revised according to their comments.

7. Publication: It was decided to publish the Persian and the English versions of the guideline in "Dermatology and Cosmetic" and "Iranian Journal of Dermatology", respectively. It should be noted that both journals are widely distributed among Iranian dermatologists who are the main audience of this guideline.

8. Update: An expert panel was appointed to to update the guideline every 3 years.

The guideline includes the definition, classification, etiology, and pathogenesis of urticaria, and practical issues related to the diagnosis and treatment of urticaria are discussed in more details.

Definition [3–5]

Urticaria is defined as erythematous, raised and pruritic skin lesions (wheal) due to the

dilation of blood vessels, increased local blood flow and vessel permeability. The size of each lesion may vary from a few millimeters to the size of the palm of the hand. As the main feature, mast cells are activated and release histamine and other inflammatory mediators. The latter in turn causes urticaria and severe skin pruritus.

Angioedema occurs as a result of increased vascular permeability and mainly involves the lips, mouth, throat, eyelids, and genitalia. Tissue inflammation in angioedema is associated with pain rather than pruritus.

Urticaria affects the superficial layers of the skin to the upper dermis (papillary dermis). However, in angioedema, the reticular dermis, and subcutaneous and submucosal layers are affected. Urticaria occurs alone in 40% of the patients whereas urticaria is accompanied by angioedema in 50% of cases. In 10% of the patients, angioedema can occur alone. In urticaria, swelling develops suddenly, reaches

its peak over a course of 8 to 12 hours, and resolves within 24 hours. However, the swelling of angioedema may persist for several days.

Clinical classification [3–5]

It is extremely difficult to classify urticaria by its causative agent. It seems to be more convenient to classify urticaria on the basis of its clinical manifestations. Based on causation, chronic urticaria can be divided in two groups: 1- Inducible, which has a specific eliciting factor; 2- Spontaneous, without any specific eliciting factor [6]. In addition, classification according to clinical features can be useful in the management of the disease. It is usually possible to differentiate different patterns of urticaria based on their clinical presentations and, if necessary, "challenge tests" and skin biopsy (Table 1). Urticaria has similar clinical features in children and adults.

1. Ordinary urticaria: It is the most common type of urticaria characterized by sudden appearance of the skin lesions in any part of the body. It may occur alone or together with angioedema. Ordinary urticaria generally occurs suddenly and spontaneously. However, in most cases, aggravating factors such as heat or clothing pressure are identified. Urticaria, with or without angioedema, which lasts more than six weeks is defined as chronic urticaria. Acute urticaria, with or without angioedema, that lasts for a few hours to a few days and recurs over time (months to years) is classified as ordinary urticaria. Even though chronic urticaria is rarely life- threatening, it can cause significant problems for the patient and reduces the patients' quality of life in such a way that makes it even comparable with cardiovascular diseases.

Table 1. Clinical classification of urticaria

Ordinary 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)
Mechanical
Delayed pressure urticaria
Symptomatic dermographism
Vibratory angioedema
Thermal
Cholinergic urticaria
Cold contact urticaria
Heat urticaria
Other cases
Aquagenic urticaria (caused by exposure to water)
Solar urticaria
Exercise-induced anaphylaxis
Angioedema without urticaria
No known cause
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

2. Physical urticaria: Unlike ordinary urticaria, physical urticarias are caused by exposure to one or more physical stimuli. If the causative stimuli are identified, changing the patient's lifestyle may reduce the number of urticaria episodes or even may prevent its occurrence. Mechanical and thermal factors are among the most common causes of physical urticaria.

3. Angioedema: Angioedema without urticaria should be differentiated from urticaria-associated angioedema. The former can occur due to C1 esterase inhibitor enzyme deficiency or using angiotensin-converting enzyme (ACE) inhibitors. Patients sometimes show abdominal pain without visible angioedema. Angioedema without urticaria may be idiopathic.

4. Contact urticaria: This type of urticaria occurs only if allergens are absorbed through the skin or mucous membranes. Contact urticaria never occurs spontaneously. Absorption of allergens through the skin or mucous membranes can cause local or systemic hypersensitivity reactions. Occurrence of contact urticaria in individuals with hypersensitivity such as severe allergic reactions to latex may result in anaphylaxis

5. Urticarial vasculitis: The lesions are clinically similar to those of ordinary urticaria. However, they are caused by the inflammation of small vessels, which can be observed on microscopic examination. Urticarial vasculitis can be a sign of certain systemic diseases and may be associated with renal and joint problems.

6. Auto-inflammatory syndromes: In auto-inflammatory syndromes, urticaria is associated with fever, malaise, and other systemic symptoms.

Muckle- Wells syndrome (MWS) that causes sensorineural hearing loss and renal amyloidosis is included, as well [7]. Hereditary cases usually occur in childhood.

Etiology [3–5]

Efficient management of chronic and acute intermittent urticaria requires comprehensive understanding of their clinical symptoms, etiology, causes, and their aggravating factors. Despite extensive studies, the specific cause of chronic urticaria remains unknown in 40% to 50% of the cases. Hence, this type of urticaria is called idiopathic, which means no known cause. Patients with chronic urticaria are often classified as clinical cases of allergies most likely due to food allergies, and efforts are made to determine the allergens. However, in most patients with chronic urticaria, food allergens are not causative agents and can be usually ruled out according to the patients' medical history.

Viral infections and, in some cases, stress are among the most common causes of the recurrence of chronic urticaria. Classification of chronic urticaria/angioedema based on the etiology of the disease is presented in Table 2.

Pathogenesis [3–5]

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 angioedema. Other mediators such as leukotrienes and prostaglandins which originate from the cell membrane are subsequently released and react on superficial tissues during the initial and final phases of 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

Table 2. Etiological classification of urticaria/chronic angioedema

Etiology of the disease	Mechanism	Examples	Investigations
No known cause (40%- 50% of cases)	Unknown		Negative
Autoimmune	IgG autoantibodies against IgE receptor on mast cells or binding of IgE to mast cells	Associated with autoimmune inflammation of thyroid	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.,.cryoglubolin
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) Angioedema Paraproteinemia- associated	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, urin alaysis, liver function tests, serological diagnosis of hepatitis B and C, immunoglobulin electrophoresis, screening for autoimmune diseases, ANCA, C3, skin biopsy
Lymphoproliferative Disorders	Paraproteinemia	B-cells lymphoma	Paraprotein in blood and urine
Food additives (rare)	Unknown	Salicylates	Stopping exposure to allergen is effective

deeper layers of the skin is more difficult to be identified and probably more mechanisms are involved. Several inflammatory mediators increase the capillary permeability. This results in plasma leakage and causes edema.

Biopsy of the lesions of autoimmune urticaria and idiopathic chronic urticaria show perivascular infiltration of CD4+ lymphocytes, monocytes, and granulocytes (neutrophils, basophils, and eosinophils). This is in contrast with the samples taken from patients with urticarial vasculitis (less than 1%), in which only small-vessel vasculitis is observed, often due to the formation of immune complexes. In some cases, only slight changes, including inflammation of endothelial cells, RBC extravasation and infiltration of white blood cells are seen.

IMMUNOLOGIC URTICARIA

1. Autoimmune urticaria

At least 30% of the patients with idiopathic chronic urticaria have histamine-releasing autoantibodies. In 40-60% of the patients with chronic urticaria, IgG antibodies against IgE receptors on mast cells are detected in adults and children.

2. Immune complex-associated urticaria

It is believed that urticarial vasculitis and drug-induced urticaria, or blood products, e.g. serum sickness, are caused by the formation of immune complexes in blood capillaries. Complement activation through C5a anaphylatoxin increases the release of histamine from mast cells.

The inflammatory cascade occurs as a result of antigen-antibody interactions and the formation of immune complexes (e.g. hepatitis B, hepatitis C, EBV, other viral infections, and some parasitic infections).

3. Allergy-associated contact urticaria

A specific IgE antibody binds to allergens such as latex gloves, eggs, dog saliva, etc. on skin mast cells. This can cause contact urticaria, anaphylaxis, and episodic acute or ordinary urticaria; however, chronic urticaria is not associated with allergies in adults. In rare cases contact with chemical compounds such as sorbic acid or benzoic acid, can directly influence the vascular walls and possibly by triggering the secretion of PGD2 causes urticaria.

4. Complement-associated urticaria

Angioedema associated with C1 esterase inhibitor deficiency is mainly caused by the formation of quinine as a result of complement activation, and the formation of bradykinin and histamine does not play a major role.

Non-immunologic urticaria

Degranulation of mast cells and basophils can occur after exposure to certain drugs such as codeine and other substances like a contrast agents used in radiology, and no IgE receptor activation is required. The mechanism of the development of urticaria or its aggravation due to the use of aspirin, non-steroidal anti-inflammatory drug (NSAID), and existing allergens like some food additives such as salicylates, azo dyes, and food preservatives still remains unclear, but probably leukotrienes and histamine release are involved. It is believed that angioedema caused by ACE inhibitors occurs due to the inhibition of quinine decomposition.

Diagnosis and assessment [3–5,7,8]

A diagnosis of urticaria is mainly based on urticaria clinical features and additional tests are only recommended in special cases and on the basis of clinical findings. No laboratory tests are required in some acute urticaria cases. In addition, there is no need to perform any laboratory test in mild chronic urticaria. In clinical history of urticaria, the items indicated in Table 3 should be considered [9].

If an underlying allergy or urticarial vasculitis is suspected, the items listed in Tables 4 and 5 should be considered for assessment [8].

The duration of individual urticarial lesions can be useful in the diagnosis of the following clinical patterns:

A) Ordinary urticaria: It usually takes urticarial lesions 2 to 24 hours to resolve.

B) Contact urticaria: The lesions last for up to 2 hours.

Table 3. Recommended history intake [73,78]

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 and emotional impact
22. Previous therapy and response to therapy
23. Previous diagnostic procedures/results

Table 4. Is there an underlying allergy? [8]

● Does urticaria occur only frequently 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, rolling on the grass, and contact with certain foods)?
● Does urticaria occur due to drugs that the patient receives (esp.: aspirin/NSAIDs/ACE inhibitors)?

Table 5. What is urticarial vasculitis? [8]

● 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 in the patient?
● Is the patient suffering from underlying symptoms such as fever, fatigue, malaise, and arthralgia?

C) Physical urticaria: Urticarial lesions disappear within an hour. However, delayed pressure urticaria appears within 2 to 6 hours and resolves within 48 hours.
D) Urticarial vasculitis: The lesions usually last for a few days.
E) Angioedema: If left untreated, it may persist for up to 3 days.

Diagnostic assessments [3,8]

A summary of the methods used in some patients with urticaria is presented in Table 6.

Recording the timing of the symptoms

Recording the time when symptoms appear after exposure to triggers is a very useful tool in diagnosing the cause of urticaria. According to the findings of the timing or the patient medical history, the following tests may be useful [8].

Complete blood count (CBC)

The test results can be a clue for identifying the cause of urticaria. For example, an increase in eosinophils occurs in parasitic infections and drug reactions, whereas a rise in neutrophils is

Table 6. Diagnostic tests recommended in common types of urticaria

Type	Subtype	Common diagnostic tests (commonly recommended)	Recommended supplementary diagnostic tests to identify underlying factors and to rule out differential diagnosis
Spontaneous urticaria	Acute and episodic spontaneous urticaria	No tests recommended	No tests required
	Chronic spontaneous urticaria	CRP, ESR, CBC	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 level measurement Stopping taking 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 urtiaria/ factitious urticaria	Dermographism test	CBC, ESR, CRP
	Aquagenic urticaria		No complementary tests required
	Cholinergenic urticaria	Wearing wet clothing at body temperature for 20 minutes	No complementary tests required
	*Contact urticaria	Prick/patch test	No complementary tests required
	Urticaria or exercise- induced anaphylaxis	Considering patient clinical history, exercise test with or without food (should not be done after hot shower	No complementary tests required

* Must be carried out and monitored in the hospital.

observed in urticarial vasculitis.

CRP/ESR

An elevated ESR can be a sign of chronic infection, vasculitis, or paraproteinemia. The CRP test can be used to assess the severity of the disease or the response to treatment [10,11].

Urinalysis

In the case of urinary tract infection as a cause of urticaria or renal involvement in urticarial vasculitis, blood or protein may be detected in the urine.

Parasitology

In case of unexplained eosinophilia or a history of travel to areas where certain parasites are common, fresh stool tests or serological investigations in particular cases are helpful in the diagnosis of the parasitic infection.

Skin biopsy

Skin biopsy is necessary if urticarial lesions last for more than 24 hours or when petechiae, purpura, and tenderness of the lesions are detected on physical examination. Skin biopsy is required if systemic symptoms such as fever, pain, or arthritis are observed, or when the lesions leave scars after they heal.

Assessment of thyroid function and anti-thyroid autoantibodies

If chronic urticaria is accompanied by thyroid antibodies in children and adults, the possibility of autoimmune urticaria arises. In these patients, the thyroid function is usually normal. However,

it is recommended to monitor them over time.

Serum complement

If angioedema occurs simultaneously with urticaria, it is not required to investigate C1 inhibitor. However, in cases of angioedema without urticaria, hereditary angioedema screening test is essential in order to measure C4 and C1 inhibitors (quantitative and functional). In urticarial vasculitis, C4 and C3 should be checked. Prognosis of urticarial vasculitis associated with hypocomplementemia is worse

Skin prick test

This test is helpful for diagnosis of suspected cases of allergic urticaria or contact urticaria. If the test results are negative, IgE-mediated allergic reactions to foods or other allergens are unlikely.

Evaluation of specific IgE

In allergic urticaria, radioallergosorbant test (RAST) or chloramphenicol (CAP) fluoroimmunoassay can detect specific IgE antibodies against specific antigens.

Autologous serum skin test

In this test, intradermal injection of the patient's own serum is done. A positive reaction as urticaria and localized discoloration indicates the presence of circulating autoantibodies against IgE receptors on the surface of mast cells. This method is a research tool, and is not widely used. The gold standard method for detection of antibodies is called basophil histamine release assay, which is available only in a limited number of centers.

Cryoglobulin

Clotted samples collected at 37° C are sent to the laboratory. The test may be positive in secondary cold urticaria.

Challenge tests

These tests are helpful in diagnosis of physical urticaria and are briefly described below.

- Cold urticaria: A piece of ice in a plastic bag is placed on the forearm for 20 minutes. Skin assessment is done after the skin warms again.
- Dermatographism: The skin is assessed through light stroking. If urticaria occurs within 10 minutes, the test is considered positive
- Aquagenic urticaria (caused by exposure to water): The test is carried out simply by immersing the body in water at 37°C for a few minutes or by placing a wet towel (with the same temperature as the body) on the skin for a few minutes
- Cholinergic urticaria: It is assessed through exercise in a hot environment. In general, no specific laboratory test is recommended for a lot of patients with urticaria. However, some tests may be required based on the symptoms. Figure 1 summarizes the diagnostic approaches to urticaria and angioedema [8].

TREATMENT

In treatment of patients with urticaria two approaches should be adopted:

Identifying and if possible, removing the factors causing or aggravating the condition; (although, this is not possible as urticaria is idiopathic in many cases) and treatment of urticaria symptoms.

A) Identification and removal of urticaria causes and / or aggravating factors

The first step in urticaria management is to identify and remove the causes or aggravating factors. A large number of patients with urticaria suffer from both chronic and physical urticaria. Therefore, in the long-term treatment, it is of great significance to identify urticaria causes and/or aggravating factors. In patients with physical urticaria, certain strategies should be adopted in order to treat the disease [12,13].

• Infection and food

In ordinary acute and chronic urticaria, treatment of infection or inflammatory diseases such as gastritis induced by *H. pylori*, or avoidance of certain food, additives and drugs may be useful in some patients [14,15]. Analgesics can cause new urticarial lesions and may also exacerbate urticaria. The role of these factors can only be confirmed if a relapse happens following a double-blind provocation test.

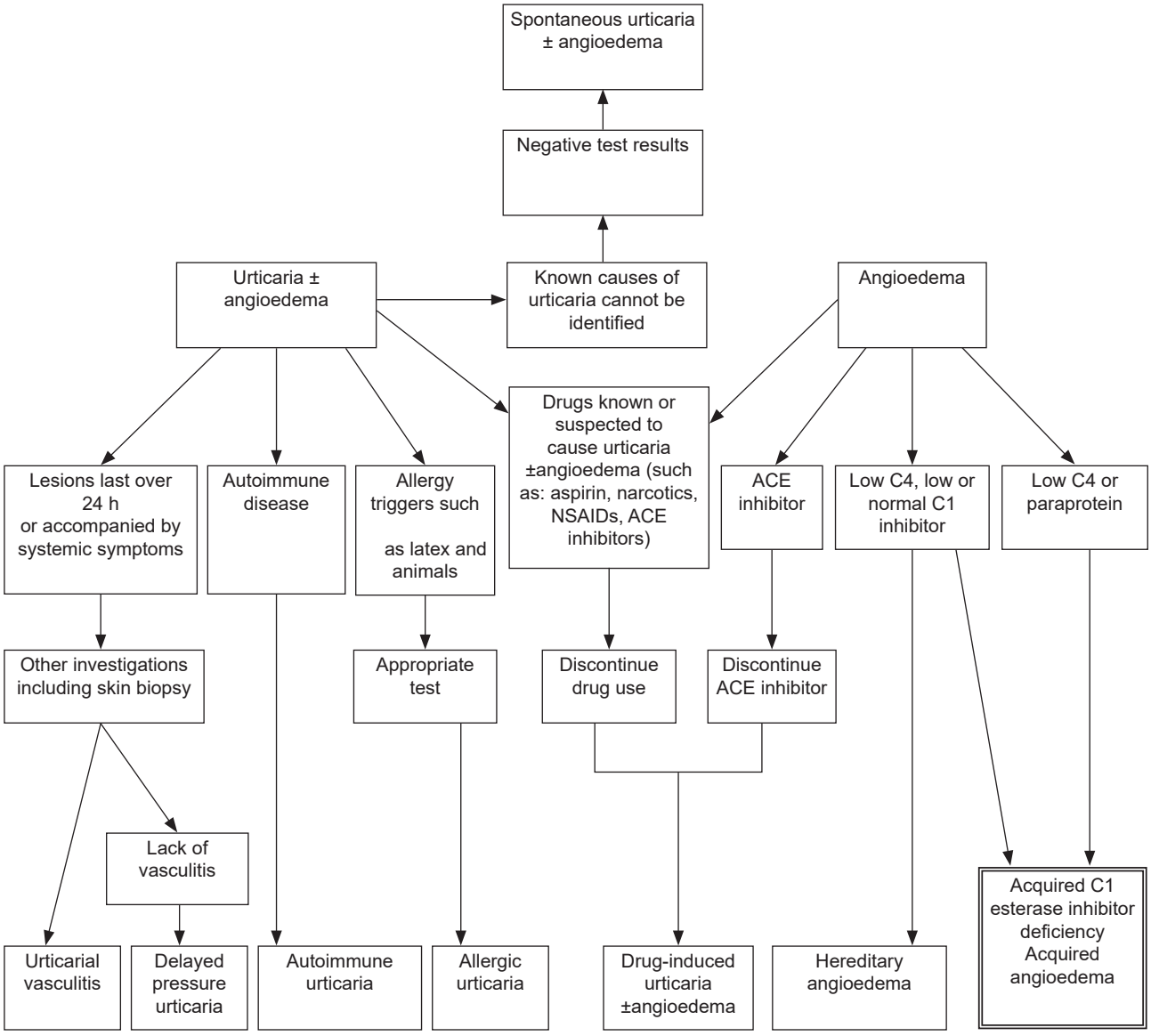

Figure 1. Diagnosis of urticaria with or without angioedema [8].

• Stress

Stress can cause or exacerbate itching in some cases of chronic urticarial [13]. Therefore, psychological counseling can be a great help to some patients.

• Drugs

Medications often cause acute urticaria. However, drugs can lead to the development of chronic urticaria as well; use of drugs that are suspected should be discontinued or they should be replaced with medications belonging to a different group.

To the extent possible, patients should refrain from taking multiple medications and unnecessary drugs should be avoided. Drugs (like aspirin) that cause IgE-independent reactions can also cause new urticarial lesions and may aggravate previous ones. In 30% of the patients with chronic urticaria, aspirin can exacerbate the disease. However, patients can usually take low-dose aspirin for anti-coagulation purposes. Therefore, in patients with chronic urticaria, aspirin and other NSAIDs are not recommended to be consumed [5,15]. Angiotensin converting enzyme inhibitors can cause angioedema, whereas they can rarely induce chronic urticaria.

However, patients with chronic urticaria (with or without angioedema) are recommended to avoid such drugs. Other drugs that aggravate chronic urticaria include narcotics (codeine, morphine), oral contraceptives, antidepressants (citalopram, statins and alcohol) [15-17].

• Physical factors

In patients with physical urticaria, accurate identification of physical factors involved and their mechanical properties is important (Table 4). However, in many patients, the threshold response to physical stimuli is very low. Therefore, it is not possible to fully control the disease [12,15].

In patients with delayed pressure urticaria or dermographism, simple measures such as using bags with wide straps could be useful in preventing the onset of the symptoms. Cold wind should be avoided in the treatment of cold urticaria. As for the treatment of solar urticaria, it is important to identify the exact wavelength of the sunlight so that suitable sunscreen and appropriate light bulbs could be provided for the patient.

• Infections

Several infectious agents can cause or aggravate urticaria:

- Viruses
- Bacteria: Dental root canal, sinus, gallbladder and urinary tract infections as well as infection with *H. pylori*
- Fungi: Fungal infections of the nails, tinea pedis, and candidiasis
- Parasites: *Strongyloides*, giardiasis, amoebiasis, and mites. Intestinal worms usually cause eosinophilia. However, the absence of eosinophilia does not rule out the infection [3,18].

• Inflammatory processes

Chronic inflammatory diseases such as chronic gastritis, reflux esophagitis, or inflammation of the gallbladder or bile ducts can also lead to the development of chronic urticaria.

• Autoimmunity

In some patients with chronic urticaria, there is an active antibody against the alpha chain of IgE receptor (FCεRI). Factors making the receptors available to antibodies can cause anaphylactic reactions. Non- immunological aggravating factors for urticaria can directly or indirectly increase the number of available receptors; therefore, antibodies can induce urticarial [19].

• Systemic diseases

Chronic urticaria could be accompanied by hyperthyroidism or hypothyroidism (Hashimoto's thyroiditis). In some patients that have no thyroid disorders but have autoantibodies, treatment with levothyroxine may lead to urticaria remission [19].

• Diet

Avoidance of pseudoallergens can help patients recover from chronic urticaria. However, severe and unnecessary diets should be avoided as well unless proved necessary. It should be noted that pseudo- allergens usually aggravate urticaria and are not causative agents.

Some patients with chronic urticaria show pseudoallergic reactions to food or food additives (including artificial colors and preservatives). A nutrient should not be consumed only if it is confirmed that it can cause urticaria.

In most patients with chronic urticaria, allergic skin or blood tests do not help with diagnosing the condition [12].

Pseudoallergen-free/food additive-free diets should be continued for 3 to 6 months; the symptoms will usually resolve in 50% of the patients during this period. It should be noted that avoiding certain foods in type I hypersensitivity (allergy that is rare in urticaria) improved urticaria within 24 to 48 hours. However, pseudoallergen-free diets should be continued for 2 to 3 weeks before urticaria could be treated. Dietary restrictions (allergens and/or pseudoallergens) are only recommended once confirmed following a double-blind provocation test [3,9,20].

• Environmental factors

Pollens, molds, sprays, animal dander, house dust mites, and smoke could all exacerbate chronic urticaria. Urticaria may be exacerbated in pregnancy

and before menstruation. Chronic urticaria due to orthopedic implants, dentures, dental amalgam used in dental fillings, and intrauterine device (IUD) has been reported. Stress, depression, and anxiety can also cause or aggravate urticarial [15,20-23].

• Contact urticaria

Contact with animals and some materials such as latex, as well as certain types of food causes urticarial lesions at the area of contact through an IgE-dependent mechanism. In this case, contact with the above- mentioned substances should be avoided so that the disease could be controlled [8].

B) Symptomatic treatment of urticaria

• Antihistamines

The term antihistamine mostly refers to H1 receptor inverse agonists that binds to the H1 receptor and inhibits the binding of histamine to the H1 receptor. As a result, the action of histamine is inhibited. The term does not usually include H2 receptor inhibitors. Antihistamines are divided into the older (first) and the new (second) generation. First-generation and second-generation antihistamines are also called sedating and non-sedating antihistamines, respectively.

First-generation antihistamines

These drugs have entered the market since the1940s and 1950s and are still considered non-prescription drugs (over-the-counter [OTC]). They are commonly used in treatment of allergic rhinitis, allergic conjunctivitis, urticaria, cough, common cold, and insomnia [9].

First generation H1-antihistamines are divided into 5 groups (Table 7). First generation drugs are relatively lipophilic; therefore, they can pass through the blood-brain barrier. First generation H1- antihistamines can cause drowsiness as a result of binding to histamine receptors in the nervous system. The drug reaches its highest concentration within 2 hours and usually binds to proteins. The drug metabolism usually occurs via hepatic cytochrome P450 enzyme, so the drug half-life may be longer in patients with liver failure as well as patients receiving medications such as erythromycin and ketoconazole that inhibit the cytochrome P450 system [24].

Such drugs are able to inhibit the symptoms of urticaria. Maximum inhibition of urticaria usually occurs when the drug reaches its highest blood concentration. Consequently, antihistamines should be used on an ongoing basis rather than whenever necessary [24].

Currently, the use of first-generation antihistamines (sedating) to treat urticaria is not recommended except in special cases. The side effects of first-generation antihistamines are listed in Table 8.

Second-generation antihistamine [24]

Like first-generation antihistamines, second-generation antihistamines are actually H1 receptor inverse agonists. The characteristic of this group of drugs is the lowest ratio of toxic to therapeutic dose or a wide therapeutic window. Therefore, in the treatment of chronic urticaria, it is possible to use these drugs at a higher than the recommended dose.

This group of drugs is less lipophilic and causes less drowsiness. They are also very selective and have fewer anticholinergic effects than the first group or do not cause these effects in some cases. Of these antihistamines, fexofenadine, loratadine, cetirizine, levocetirizine and desloratadine are available on the market. Terfenadine and astemizole have been withdrawn from the market due to their cardiovascular complications such as increasing the Q-T interval.

Table 7. The main groups of first-generation antihistamines and examples of each group [9].

Group	Example
Ethanolamines	Diphenhydramine
Piperidins	Cyproheptadine
Phenothiazines	Promethazine
Alkylamines	Chlorpheniramine
Piperazines	Hydroxyzine

Table 8. Side effects of first-generation antihistamines

Affected system	Side Effects
Central nervous system	Drowsiness, impaired cognitive function, increased appetite
Digestive tract	Dry mouth, Constipation
Genitourinary tract	Dysuria, erectile dysfunction
Cardiovascular system	Tachycardia, arrhythmia
Other side effects	Diplopia

The generic name, brand name, formulation and dosage, and recommended dose of second-generation H1 receptor inhibitor antihistamines in Iran for adults are presented in Table 9 and their pharmacokinetic characteristics are presented in Table 10.

Fexofenadine

Like other second-generation antihistamines, fexofenadine is an H1 receptor inverse agonist, is selective, and its side effects are not different from placebo. Although this drug is derived from terfenadine, it does not have a liver metabolism, and is excreted almost intact. Fexofenadine does not have anticholinergic effects and several studies on humans and animals have indicated its safe cardiovascular profile [24].

Driving and other activities that require alertness are not affected by fexofenadine and it increases the patient's quality of life. The safety of this drug in children, patients with liver failure or renal disease, and the elderly is known and the dose in these patients does not need to be adjusted. Fexofenadine does not cause drowsiness and drowsiness is not observed even at higher than recommended doses. No report is available regarding drug resistance [25].

Fexofenadine is rapidly absorbed after oral administration and acts dramatically faster than loratadine. Within 1 to 3 hours, the drug reaches its maximum blood concentration and its effects last for up to 24 hours [26].

Scientific evidence suggests that oral administration of 180 mg once daily is effective for the treatment of chronic urticaria [27]. No clinically significant drug interactions have been reported yet [28].

Loratadine

Loratadine is a new generation antihistamine of the piperidine group. At the recommended dose, loratadine anticholinergic effects, sleepiness, and other side effects are minimal. The active metabolite of this drug is desloratadine. The drug has a half-life of 8 to 11 hours. Even though liver and kidney dysfunction has no significant impact on the pharmacokinetics of the drug, the drug dose adjustment is necessary in patients with chronic liver and kidney problems. Often a single oral dose of 10 mg inhibits the symptoms of urticaria for 12 hours. Unresponsiveness to the drug has

Table 9. Generic name, brand name, dosage form and recommended dose for adults' second-generation H1 receptor inhibitor antihistamines in Iran

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

Table 10. Pharmacokinetic characteristics of second-generation H1 receptor inhibitor antihistamines in Iran [19].

Name	Time to maximum serum level (hours)	Bioavailability (%)	Binding to protein (%)	Half-life (hours)	Active metabolite	Excretion
Fexofenadine	1-3	85	60-70	14.4	Terfenadine premedication	80% in the feces
Cetirizine	0.5-1.5	70	93	8.3	Levocetirizine	More than 70% through urine
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
Desloratadine	3	100	82-87	27	Desloratadine	negligible urinary excretion

not been reported yet [24].

Although loratadine affects potassium channels, it does not cause cardiac arrhythmia. This medication has no interaction with drugs affecting cytochrome P450 3A4 (CyP3A4). The drug is mainly used for the treatment of chronic urticaria [29,30].

Cetirizine

Cetirizine is hydroxyzine carboxylic acid metabolite. Oral administration of a single dose of 10 mg can alleviate the symptoms of urticaria for up to 24 hours. Anticholinergic symptoms would be minimal at the recommended dose. According to some studies, drowsiness is observed in 13.7% of the patients following taking the recommended dose, while 6.3% of the patients in the placebo group experience this complication. The frequency of this complication increases at higher doses. In patients with chronic renal or liver problems, adjusting its dose to 5 mg is recommended. Cetirizine can be used for the treatment of chronic urticaria. So far, significant drug interactions and side effects such as cardiotoxicity have not been reported [25,31–33].

Levocetirizine

Levocetirizine is the R-enantiomer of cetirizine and its major metabolite. It seems to be more effective than loratadine in suppressing urticaria. Its anticholinergic effects and drowsiness are very slight. It is recommended for the treatment of urticaria in patients above 6 years old and a daily dose of 5 mg is recommended [34,35].

Desloratadine

This drug is the active metabolite of loratadine which is absorbed rapidly from gastrointestinal tract and is similar to loratadine in efficacy and safety.

Antihistamines in special cases

Renal failure: Patients with renal impairment should take half the dose of cetirizine, levocetirizine, and hydroxyzine.

Hepatic failure

Chlorpheniramine and hydroxyzine are not recommended in these patients [4,24].

Pregnancy and lactation

Although not proven to be teratogenic, antihistamines are not recommended during the first trimester of pregnancy. According to manufacturers, hydroxyzine is the only antihistamine that is prohibited in the early stages of pregnancy. Being known as safe for a longer period of time, chlorpheniramine is recommended in these cases. Although loratadine and cetirizine are not proven to be safe during pregnancy, these drugs are categorized as group B. Thus, there is no evidence available regarding their side effects on the fetus during pregnancy [35,36].

Childhood

None of the antihistamines that have been licensed so far are prohibited in children aged 12 years or above. Since the age limit and dose for each of the antihistamines in children less than 12 years of age is different, it is better to refer to the respective information prior to drug administration [3].

Diphenhydramine, hydroxyzine, promethazine, chlorpheniramine are licensed for use in children. Chlorpheniramine and hydroxyzine can be used in children under 2 years old. Even though children become accustomed to the hypnotic effect of drugs, psychomotor disturbance may result in impaired performance of the children at school. Cyproheptadine is effective in children, especially in cold urticaria. However, it increases the appetite [24].

Cetirizine and loratadine are licensed for the treatment of urticaria in children above 2 years old. Fexofenadine and levocetirizine are licensed in children above 6 years. The use of cetirizine in 1- to 2-year- old children at a dose of 0.25 mg per kilogram of body weight 2 times a day has been reported to be safe and harmless [24].

• Other drugs

These drugs are the last line of drug therapy for the treatment of chronic urticaria. They are allowed only in cases that treatment with antihistamines at maximum doses is not effective. No sufficient data is available on the effectiveness and side effects

of the long-term use of these drugs, which has to be explained to the patients clearly [37,38].

H2 receptor antagonists

The use of a combination of an H1-inhibitor antihistamine and an H2-blocker antihistamine such as cimetidine or ranitidine has probably only a slight effect. These drugs are simultaneously used in patients who have digestive problems and use corticosteroids [23,24].

The therapeutic approach to urticaria is summarized as an algorithm in Figure 2.

Doxepin

Doxepin is a tricyclic antidepressant that is capable of acting as an antihistamine. Oral administration has been proven effective for the treatment of severe urticaria [39]. Doxepin is prescribed with a dose of 10 to 25 mg once a day [40].

Cyclosporine

Cyclosporine is a cyclic polypeptide consisting of 11 amino acids. It is an immunosuppressive drug that suppresses humoral and mainly cell- mediated immunity. It is used to treat a range of immune reactions such as allograft rejection, delayed hypersensitivity, and graft versus host disease (GVHD). T cells are selectively inhibited and the production and release of lymphokines, including interleukin-2 (IL-2) and T cell growth factor (TCGF), can be inhibited by the drug. Cyclosporine is used as a successful therapy for the treatment of chronic urticaria via inhibiting the release of histamine, leukotriene C4, and other mast cell mediators [41–43]. Cyclosporine is designated in the C category for pregnancy and is prescribed with a dose of 3-5 mg/kg daily in two divided doses [44].

Omalizumab

Omalizumab is a humanized IgG1 monoclonal antibody that selectively prevents the binding of IgE molecules to mast cell and basophil IgE receptors, and has been proven to be a safe and effective treatment modality in the treatment of CSU patients refractory to antihistamines [45–49]. It is being used since 2014 for the treatment of CSU in the United States and Europe for patients over the age of 12 years, and refractory to standard of care. The benefits of omalizumab treatment can be seen since the first week in some in some patients [50], but patients must be informed that the improvement in their symptoms may not be evident immediately [51].

For chronic urticaria, omalizumab is prescribed at doses of 150 or 300 mg- irrespective of patient's weight and/or the IgE level in serum- as subcutaneous injections every 4 weeks [52]. The licensed dose and the duration of the treatment is different in different countries, but evidence shows that the 300 mg dose has the highest efficacy and chances of getting response goes higher with at least 3 injections [50]. Omalizumab has also shown efficacy in the treatment of other physical mechanical urticaria [53,54], including cholinergic urticaria [55], cold urticaria [56], solar urticaria [57], heat urticarial [58], dermographic/induced urticaria [59], and also delayed pressure urticaria [60]. In cases of relapse after withdrawal from the treatment, patients can benefit from retreatment with omalizumab [61,62].

Omalizumab is considered a safe product. The incidence and severity of adverse events and serious adverse events were low and similar to the placebo group in clinical studies [45–47]. Although upon the drug's entry to the market, there were initial concerns about increasing chance of malignancy with omalizumab therapy [63], current data has shown no association between omalizumab and malignancy [64–66]. Among the reported adverse events, a rare but important event, is the potential risk of anaphylaxis, which can happen in 0.1 – 0.2% of patients [67]. A significant percentage of the patients that experienced anaphylactic shock, due to omalizumab had a previous non-omalizumab relevant shock and the underlying reason is not clear [67]. Omalizumab must be administered by a trained person at a setting with proper facilities, who can manage the patient in case of appearance of the symptoms of anaphylaxis.

For chronic urticaria patients, there are no mandatory blood tests to determine dosage or injection times, prior to prescribing the medication [51]. Omalizumab is a category B drug in pregnancy, and can safely be used in pregnant patients, and there are no reports of teratogenicity yet [68-70].

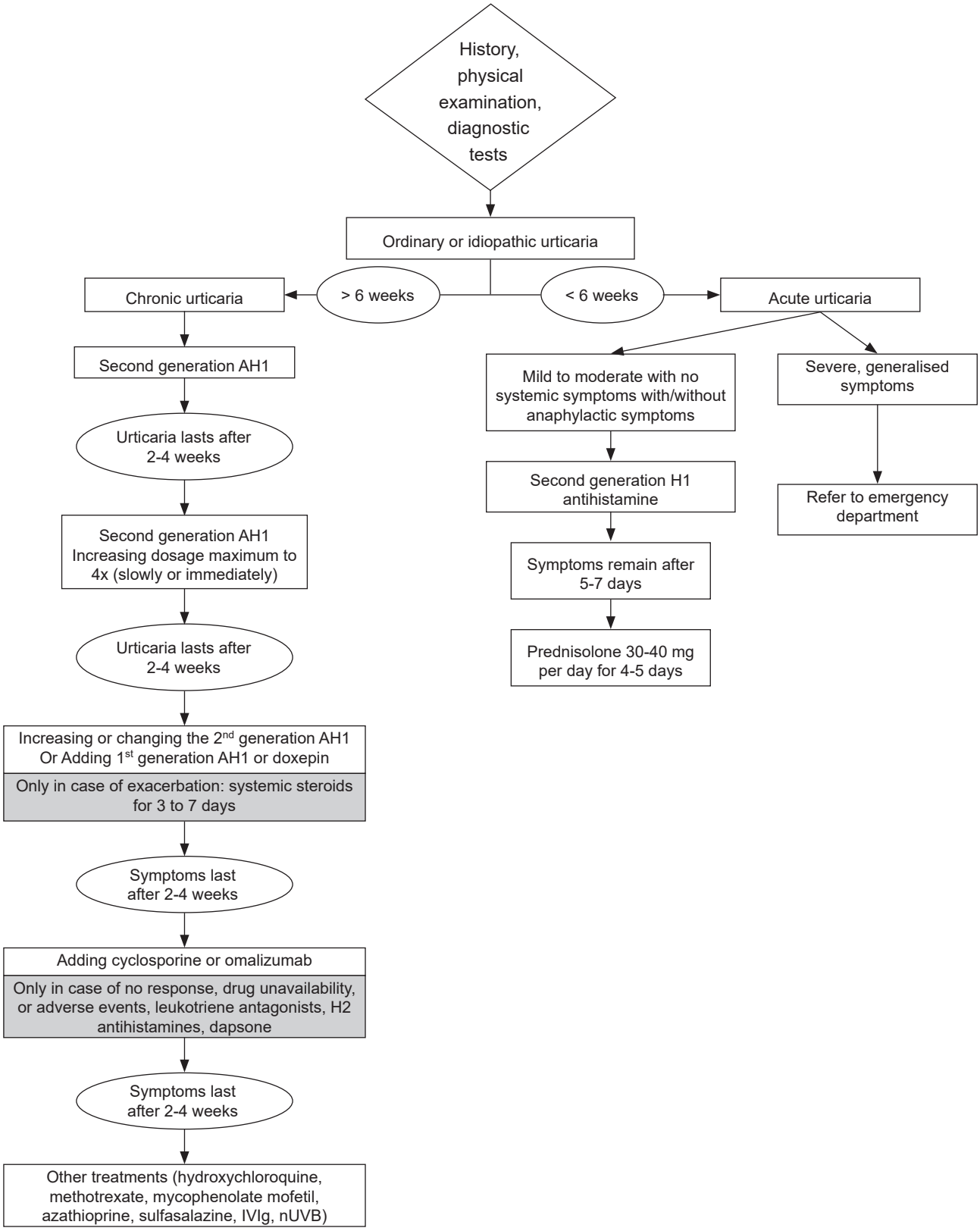

Figure 2. Algorithm of urticaria treatment

Dapsone

Dapsone is a sulfone derivative with antimicrobial and anti-inflammatory functions. This drug has been used for more than 80 years to treat a range of skin diseases, including infections such as leprosy. Dapsone alone or in combination with other drugs is used for the treatment of chronic idiopathic urticaria [71,72]. The initial dose of dapsone is 100 mg per day, which can be tapered gradually according to the patient's response to treatment.

Montelukast

A leukotriene receptor antagonist used for treatment of chronic idiopathic urticaria. Several studies have provided different reports on its effectiveness. According to a randomized double-blind study in which the efficacy of an oral dose of 10 mg daily was compared with that of 5 mg levocetririzine per day, the efficacy of both treatment options in chronic idiopathic urticaria was similar but the drowsiness was lower and the quality of life was higher for levocetrizine [73]. In a more recent study, a combination of montelukast at the above-mentioned dose and an antihistamine significantly reduced the symptoms in patients with severe refractory chronic idiopathic urticaria, as compared to the placebo [74]. It is generally prescribed as 10 mg daily dose [44].

Miscellaneous drugs:

In chronic urticaria cases refractory to the above treatments, or in case of adverse events, non- tolerability, or contraindications, it is possible to prescribe the following drugs, however, there is no evidence of their effectiveness: azathioprine, mycophenolate mofetil, methotrexate, hydroxychloroquine, IVIG and sulfasalazine [37].

• Non-drug therapies and alternative approaches

When urticarial lesions appear, a lukewarm shower and the use of skin soothing ingredients such as creams or solutions containing 0.5% to 1% menthol or calamine and 10% crotamiton solution can help. PUVA has been used in the treatment of chronic urticaria. Although it has not been shown to be effective, the response to NBUVB has been better [75]. Considering the prevalence of psychological symptoms in patients with chronic urticaria, it seems that a complementary therapy should be used for patients suffering from psychological issues [24,76].

Treatment response assessment

Based on the duration of the disease and how it changes with time it is better to use a measurement tool to assess the severity of the disease and the response to treatment. The most comment tools for this are the Dermatology Life Quality Index (DLQI) and Urticaria Activity Score over 7 Days (UAS7) (attachment 1) [77].

Acknowledgment

The development of this practical clinical guideline was funded by Novartis Pharma Services Company, Iran. The guideline development committee members express their sincere gratitude to the medical unit of the Novartis Company, Iran, especially Dr. Laleh AtashbarAzar for her continuous support.

Conflict of Interest

The preparation of this guideline has been sponsored by Novartis Pharma Services AG, Iran Branch. In addition, Yasaman Norouzi is an employee of Novartis Pharma Services AG, Iran Branch.

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