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Chapter

Approach to Chronic Urticaria from Primary Care and Emergency Services: Case Reports in Spain

Luis Geniz Rubio, Macarena Ávila Pérez, José Ángel López Díaz and Sara Alcántara Luna

Abstract

Urticaria is a common process. The true incidence is not known; it is believed that between 15 and 25% of the population may suffer at some point in his life. Acute urticaria has a prevalence of 20% and the chronic form 0.5–1%. Urticaria is a disease that affects the skin and mucosa, characterized by the presence of hives. It occurs as a localized intracutaneous edema circled and an area of redness (erythema), which is typically itchy. There are histaminergic foods and drugs that worsen the prognosis of the disease. Foods which rely on aging to taste nice are always presumed to be high in histamine (chocolate, yogurt, seafood, strawberries, etc.) and drugs like nonsteroidal anti-inflammatory drugs. For diagnosis we have several tools (urticarial activity score, chronic urticaria quality-of-life questionnaire (CU-Q2oL), urticaria control test, etc., among which the most useful, simple, and cost-effective is the clinic history). The treatment of choice are antihistamines, from a daily tablet up to four tablets as maximum dose. Corticosteroids are excluded to exacerbations and must be prescribed in short guideline (maximum 10 days) without progressive decrease. Severe forms of urticaria resistant to treatment with antihistamines are treated with biological agents like omalizumab.

Keywords: urticaria, hives, itching, angioedema, antihistamines

1. Introduction

The interest in making this chapter was to explain the pathology of chronic urticaria as prevalent and its high morbidity.

We often see this problem in our primary care consultations and emergency services, so we consider its important to make a chapter about urticaria.

The current version of the EAACI/GA^{2}LEN/EDF/WAO urticaria guideline from 2018 contains new aspects about diagnosis and treatment.

At the end of the chapter, we show a series of cases treated in our practice (observed in a Juan Ramon Jimenez's dermatology room in Huelva, Spain), exposing results obtained with the different forms of treatment (**Figure 1**).



Figure 1.
Chronic urticaria.

2. Epidemiology

Urticaria is a common process. Although the true incidence is not known, it is believed that between 15 and 25% of the population may suffer at some point in his life. Acute urticaria has a prevalence of 20% and the chronic form 0.5–1% [1]. Age, race, sex, occupation, geographical region, and the season of the year may be implicated in urticaria and angioedema. The majority of acute episodes are due to adverse reactions to medications or food or, in children, to viral diseases.

Spontaneous chronic urticaria represents about 70% of all chronic hives and may persist for several years. Patients with chronic urticaria often describe a decrease in the quality of life because of itching and may have alterations of sleep, fatigue, social isolation, or emotional disorders (**Figures 2–4**).

2.1 Physiopathology

Urticaria is a disease that affects the skin and mucosa, characterized by the presence of hives. It is a localized intracutaneous edema that circled an area of redness (erythema), which is typically itchy. Individual hives can persist from 30 minutes to 36 hours and can measure from only 1 millimeter up to 15–20 cm in diameter, named giant hives [2]. Increased dilation and permeability of blood vessels that characterize the hives are present in the superficial dermis and undertake the venous plexus located there (**Figure 5**). It is rare and it may occur with concomitant angioedema.

Another similar entity is angioedema, with a similar mechanism as urticaria [3], but the pathology is located in the deep dermis and subcutaneous tissue, and swelling is the main manifestation. The skin may be normal or erythematous. There is less itching, but it can cause pain or burning sensation. The mouth, lips, eyes, throat, feet, and hands are most commonly affected (**Figures 6** and 7). When angioedema affects the throat, it can be life-threatening, because there is interference in

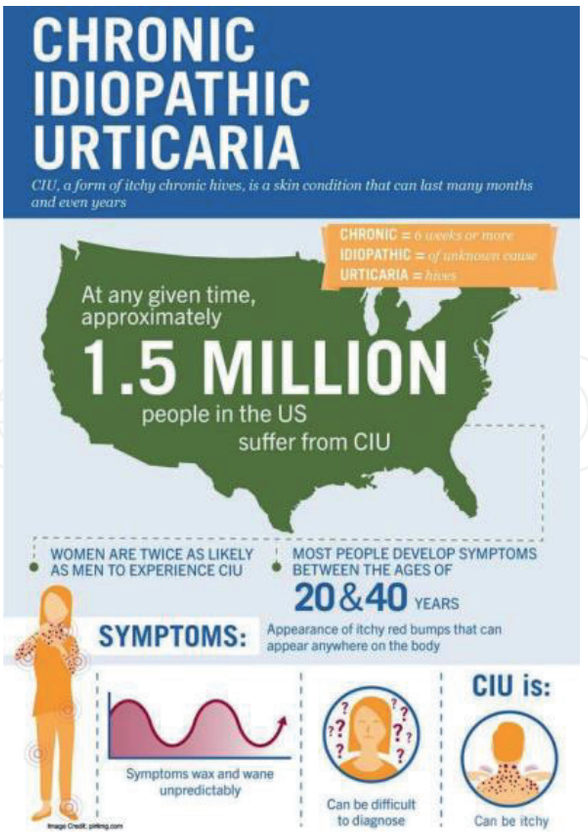


Figure 2.
Epidemiology of chronic urticaria in United States.

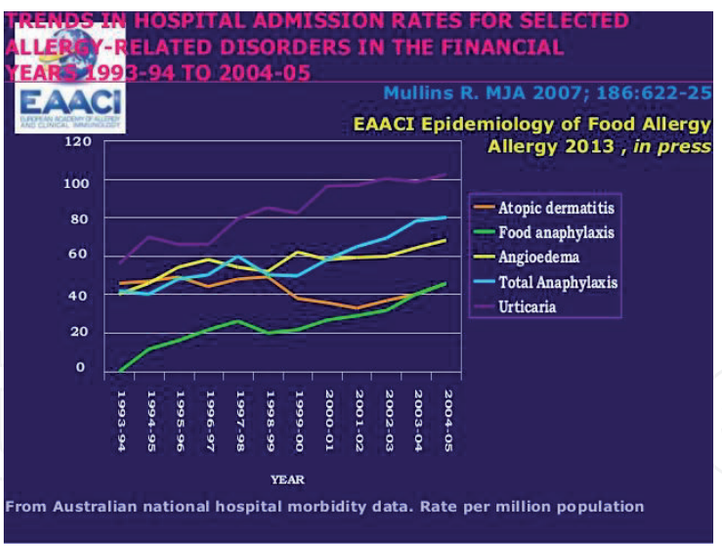


Figure 3.
Epidemiology of chronic urticaria in Australia.

breathing. It is caused by an allergic reaction, sometimes by a hereditary condition (hereditary angioedema), but normally we do not know the cause [3].

2.2 Food histamine liberator

Foods that require a ripening process to achieve a better taste are presumed to have a high histamine content. In the same way as foods that are made during fermentation. These include de following [4] (**Table 1**).

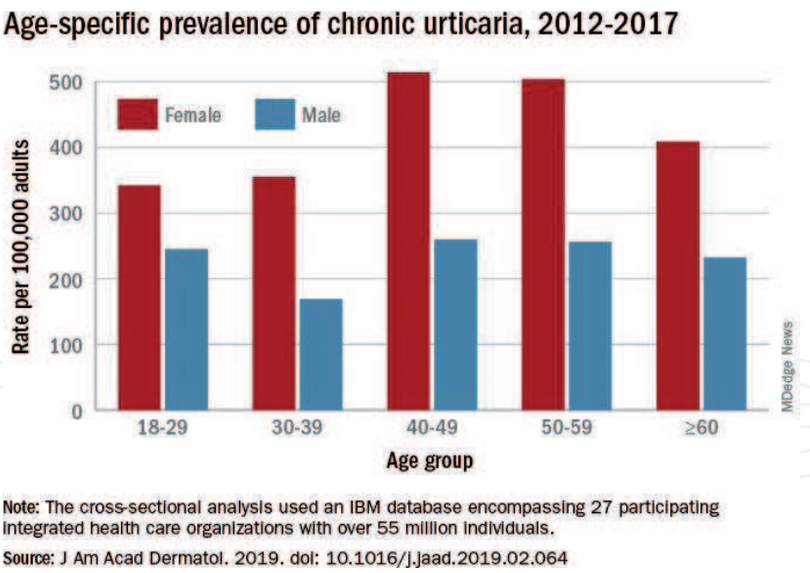


Figure 4.
Prevalence of chronic urticaria.

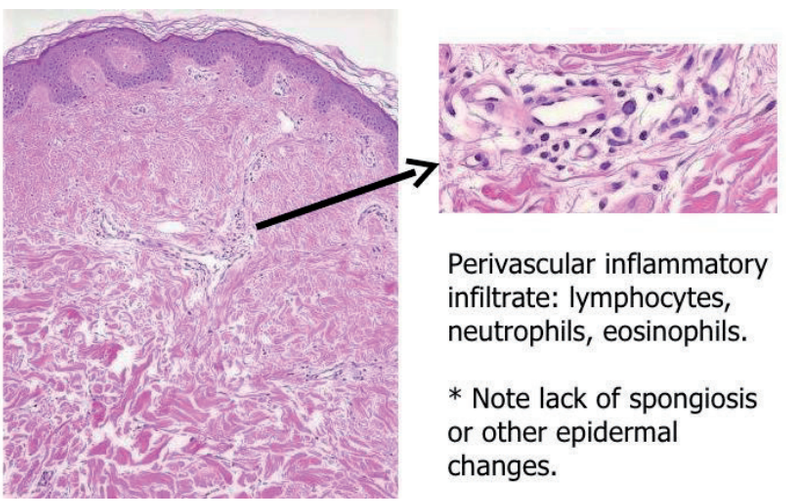


Figure 5.
Urticaria. Picture with histological findings.

The Spanish society of diamine oxidase (DAO) states on their website that the following food histamine liberators:

- Alcohol, citrus fruits, strawberries, pineapple, kiwi, tomato sauce, seafood, chocolate, fish, mushrooms, pig, cereals, and egg white.

- Some food additives such as glutamate, benzoate, several colorants (yellow E-102 and E-110, E-124, amaranth E-123), sulfites, and nitrites can release endogenous histamine.

The department for dermatology in Bonn's paper lists the following foods as being capable of releasing endogenous histamine (**Table 2**).

2.3 Pathogenesis

The mast cell is the main effector cell in urticaria and angioedema. Cutaneous mast cells attach to fibronectin and laminin through the integrin beta1 of Very Late



Figure 6.
Angioedema.

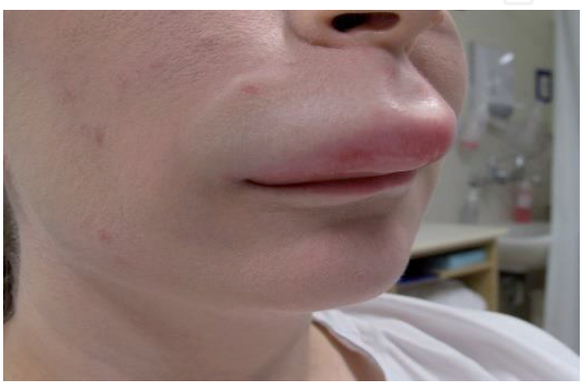


Figure 7.
Angioedema.

Yogurt	Soured cream
Buttermilk	Quark
Cottage cheese	Alcohol
Hard cheeses, cheddar	Vinegar
Aged cheeses, brie	Sauerkraut

Table 1.
Histamine liberator food.

Antigen (VLA), VLA-3, VLA-4, and VLA-5 activation and vitronectin through alfa1 and beta3 integrin [5].

Once activated, the mast cell releases granules containing histamine and other mediators of inflammation such as platelet activating factor (PAF) from, TNF alpha, IL-3, IL-4, IL-5, IL-6, IL-8, IL-13, GM-CSF, PGD-2, and leukotrienes (LTC4, LTD4, LTEA). Histamine, TNF alpha, and IL-8 also stimulate endothelial adhesion molecules that favors the migration of eosinophils, monocytes, and neutrophils from the bloodstream to the skin.

Histamine is an amine vasoactive located in granules of mast cells [5], basophils, and platelets. Its effects on the skin are mediated through histamine H1 and H2 receptors. H1 receptors mediate urticaria vasodilation, increased vascular permeability, and sensory nerve stimulation. Sensory nerve stimulation determines the release of neuropeptides such as substance P, peptide vasoactive intestinal (VIP), and somatostatin, which in turn induce the mast cell activation and increase in histamine.

Citrus fruit	Chocolate
Papaya	Fish
Strawberries	Crustaceans
Pineapple	Pork
Nuts	Egg white
Peanuts	Additives
Tomatoes	Liquorice
Spinach	Spices

Table 2.
Foods as being capable of releasing endogenous histamine.

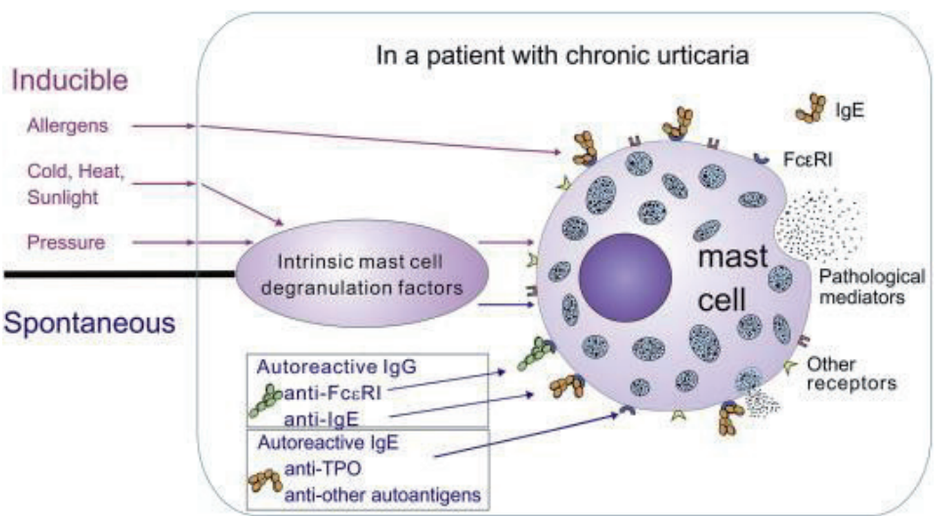


Figure 8.
Physiopathology of urticaria. Note like that the mast cells are the principal cells implicated.

The vascular endothelium expressed a significant number of H2 receptors, so the vascular response in the UC is an immunomodulatory effect, to increase the synthesis of pro-inflammatory cytokines such as IL-1 and IL-6 of monocytes and IL-6 and IL-8 cell endothelial. In addition to histamine, other soluble factors synthesized by mast cells contribute to the increase of vascular dilation and permeability; favor chemotaxis, cell activation of leukocyte, and endothelial cells; and induce stimulation sensory. These are the cytokines, chemokines, and neuropeptides and arachidonic acid metabolites.

The degranulation is attributed to immunological causes (autoimmune, IgE-dependent, immune complexes, complement-dependent), not immune (pseudo-allergies, agents release by mast cells) and idiopathic. The path of the synthesis of prostaglandins and leukotrienes, hours later the mast cell activation, occurs in the synthesis of leukotrienes and prostaglandins from arachidonic acid via two-way enzymatic metabolism: the cyclooxygenase path and the lipoxygenase pathways.

Studies have shown that LTB4 has a potent chemotactic activity, which is produced by mast cells in the early and selective recruitment of leukocytes. At chronic urticaria (CU), these mediators appear to be the most important in the chronicity of the disease. There are no immune reactions (pseudoallergics); the mechanisms are not clear but may compromise the metabolism of arachidonic acid, prostaglandins, and leukotrienes [2] (**Figure 8**).

3. Classification

According to the time evolution, urticaria can be divided into:

- Acute urticaria: less than 6 weeks.
- Chronic urticaria*: lesions appear for more than 6 weeks [6].

Recurrent urticaria: outbreaks recur over time, but its duration is limited. Episodes of hives last less than asymptomatic intervals.

* Chronic urticaria is divided into two:

Spontaneous chronic urticaria: spontaneous emergence of hives, angioedema, or both for longer than 6 weeks, due to a known or unknown cause.

Inducible urticaria: physical urticarial (This hives occur at the site of the stimulation)l, cholinergic, aquagenic and contact urticarias (**Figure 9**).

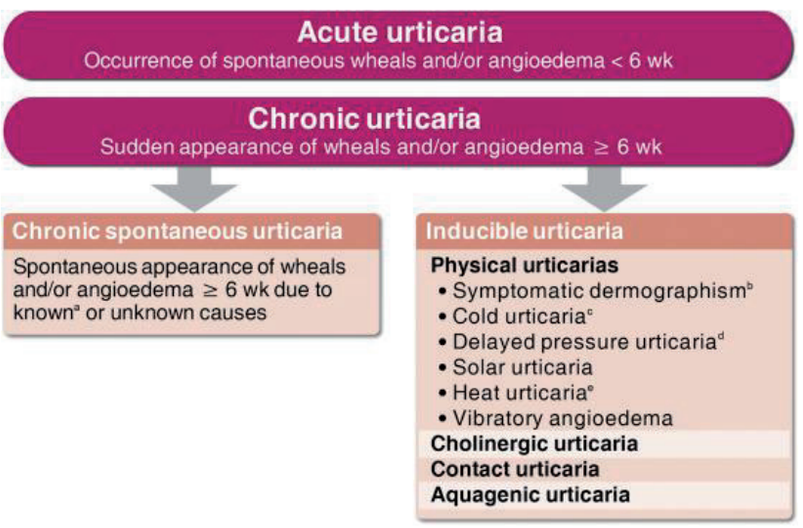


Figure 9.
Acute and chronic urticaria.

4. Symptomatology

Urticaria typically presents well circumscribed wheals (polimorphyc, serpenginous or round), with intensely pruritic for less than 24 hours of evolution. Wheals can be generalized, including arms, legs, face. Urticaria +/– angioedema (primarily in the face), can be acute (with an evolution of less than 6 weeks), or chronic (greater than 6 weeks [7] (**Figures 10–15**).

5. Diagnosis

For diagnosis we have several tools, among which the most useful, simple, and cost-effective is the clinical history, but we can ask for additional tests in the case of diagnostic doubt or suspicion of systemic disease [8].

5.1 Clinical history

A detailed clinical history and a good physical examination of the patient are necessary to make the diagnosis.

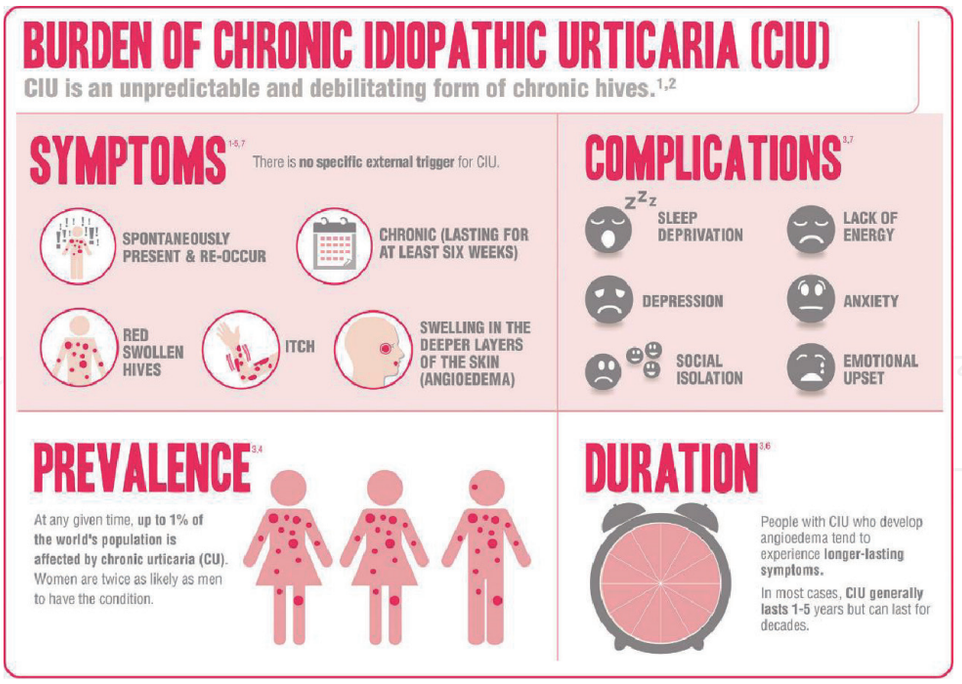


Figure 10.
Generalities of urticaria.



Figure 11.
Dermatological manifestations of urticaria. Note the typical hives.



Figure 12.
Dermatological manifestations of urticaria. Note the erythema.

Thanks to its history, we can classify chronic urticaria as spontaneous or inducible. For this, we must focus on the following aspects:

- A family history of atopy or urticaria.
- Commonly used drugs and relation with the hives.

- A history of allergies, infections, or any other cause that has been able to trigger hives.
- Work performed and hobbies.
- Induction of urticaria due to exercise or exposure to physical agents.
- How the body reacts to insect bites.
- If the patient has been on holidays or trip recently.
- If it has relationship with the menstrual cycle or stress.
- If the quality of life is affected.
- Duration of the disease.
- Frequency and duration of the hives, size, shape, and distribution.
- If associated symptoms are subjective such as pain, burning, etc.
- If the patient has nocturnal or diurnal variation.
- How the response was to the treatments used.

5.2 Complementary tests

Complementary tests serve as support to the diagnosis, to detect associated systemic diseases or for differential diagnosis.

Basic laboratory tests, as blood count and biochemical reaction (determination of C-reactive protein, glomerular sedimentation rate), can help us rule out there is a systemic disease. The baseline of tryptase, antithyroid antibodies, and thyroid profile and study of complement and specific IgE where allergy is suspected, could also be useful. If an infection cause is suspected, hepatitis B and C virus or Helicobacter Pylori could be detected.

New guidelines recommend not to perform additional exploration in a systematic way in acute urticaria and just a complete blood count with ESR and a suspension of nonsteroidal anti-inflammatory drugs (NSAIDs) in the CU (**Figure 16**).



Figure 13.
Linear hives made by compression.



Figure 14.
Coalescing urticarial papules.



Figure 15.
Urticaria and angioedema.

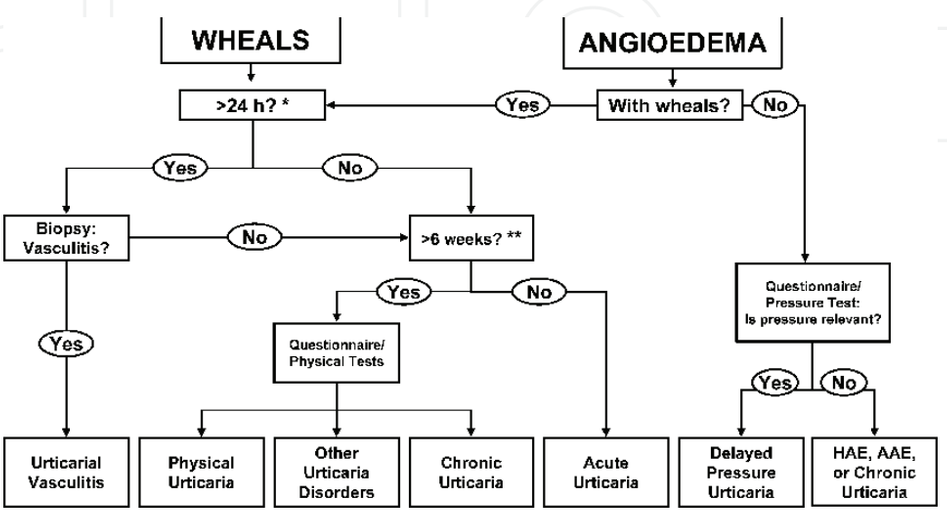


Figure 16.
Diagnosis algorithm.

6. Treatment

Different ways are approached for the treatment of urticaria: eliminating histaminergic food such as seafoods, canned goods, tomatoes, strawberries, bananas, pineapple, or apples and avoiding nonsteroidal anti-inflammatory drugs (NSAIDs) [9], nonsedative H1-antihistamines, and in severe cases systemic corticosteroids [10].

6.1 Mild forms of urticaria

- The treatment of choice are antihistamines, from a daily tablet up to four tablets as maximum dose.
- Corticosteroids are excluded for exacerbations and must be prescribed in short guideline (maximum 10 days) without progressive decrease.
- Avoid taking NSAIDs.

6.2 Severe forms of urticaria or exacerbations and associated angioedema

- Nonsedative H1-antihistamines to full dose (four tablets in a day) [11].
- Systemic corticoids, preferably in short treatment (10-day short guideline).
- Forms resistant to treatment: biological agents (omalizumab*).
- Avoid taking NSAIDs (**Figure 17**).

*Omalizumab is a recombinant humanized monoclonal antibody, which blocks the high-affinity Fc receptor of IgE (**Figure 18**). It has been approved for treatment in cases of moderate-to-severe asthma, but it has promising results in the management also of chronic urticaria [12]. The dose is 150 or 300 mg by subcutaneous injection every 4 weeks. Dosing is not dependent on body weight or serum IgE level. The appropriate duration for CIU has not been evaluated yet. It's necessary to periodically reassess the need for continued therapy with omalizumab [13].

6.2.1 Clinical guidelines

The European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA2LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) and the American Academy of Allergy, Asthma, and Immunology (AAAAI) have some differences in their recommendations for urticaria treatment, but the core recommendations remain similar.

A brief summary of *AAAAI guidelines* are as follows [14]:

As first-line treatment, second-generation nonsedating H1 antihistamines.

Remain in the treatment algorithm first-generation H 1 antihistamines (differs from EAACI/GA 2LEN/EDF/WAO guidelines).

Second-line options to consider: adding other second-generation H 1 antihistamines, up-dosing second-generation H 1 antihistamines, leukotriene receptor

Efficacy of increased doses of non-sedating antihistamines in patients with chronic urticaria

Author [ref]	Drug	Dose (mg)	Efficacy Responders/n	%
Finn [17]	Fexofenadine	120 BD	46/89	51.6
Finn [17]	Fexofenadine	240 BD	54/83	64.9
Nelson [18]	Fexofenadine	120 BD	33/77	42.8
Nelson [18]	Fexofenadine	240 BD	46/82	56.0
Giménez-Arnau [19]	Rupatadine	20 QD	69/109	63.3
Dubertret [20]	Rupatadine	20 QD	48/67	71.6
Siebenhaar [21]	Desloratadine	20 QD	15/30	50.0
Staevska [22]	Desloratadine	10 QD	7/36	19.4
Staevska [22]	Desloratadine	20 QD	1/29	3.4
Staevska [22]	Levocetirizine	10 QD	8/31	25.8
Staevska [22]	Levocetirizine	20 QD	5/23	21.7
Krause [23]	Bilastine	40 QD	11/20	55.0
Krause [23]	Bilastine	80 QD	12/20	60.0

Figure 17.
Nonsedative antihistamines.

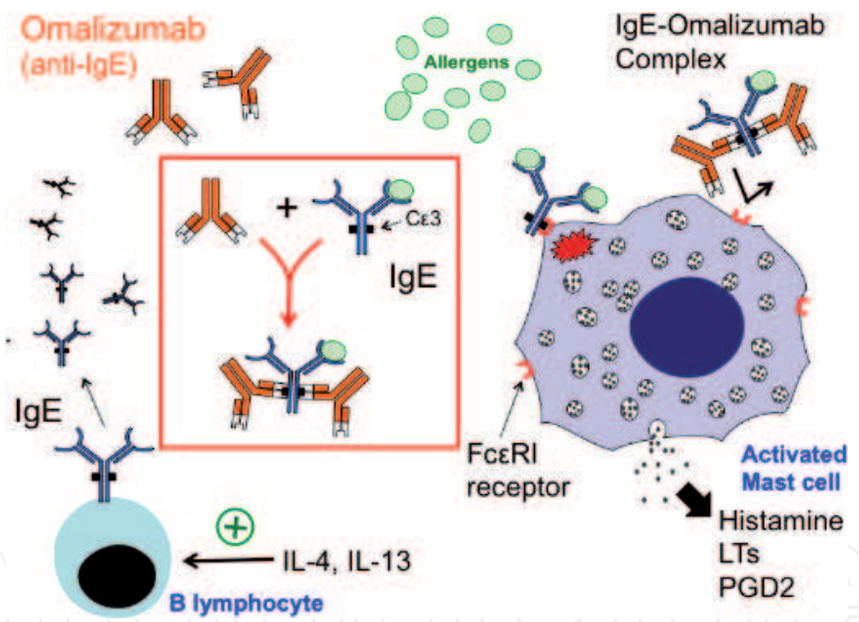


Figure 18.
*Monoclonal antibody that binds to the Cε3 domain of circulating IgE, which prevents IgE from binding to and activating receptors in mast cells (***Figure 19***).*

antagonists, adding H 2 antagonists or first-generation H 1 antihistamines at bedtime.

Omalizumab as third-line treatment.

Corticosteroids considered only for short treatment.

Cyclosporine A* is used in refractory chronic urticaria not responsive to other treatments.

A brief summary of *EAACI/GA2LEN/EDF/WAO guidelines* are as follows:

First-line treatment, second-generation H 1 antihistamines.

Up-dosing second-generation H1 antihistamines are the second-line therapy.

Omalizumab is the third-line treatment, which is recommended because it is less toxic than cyclosporine A.

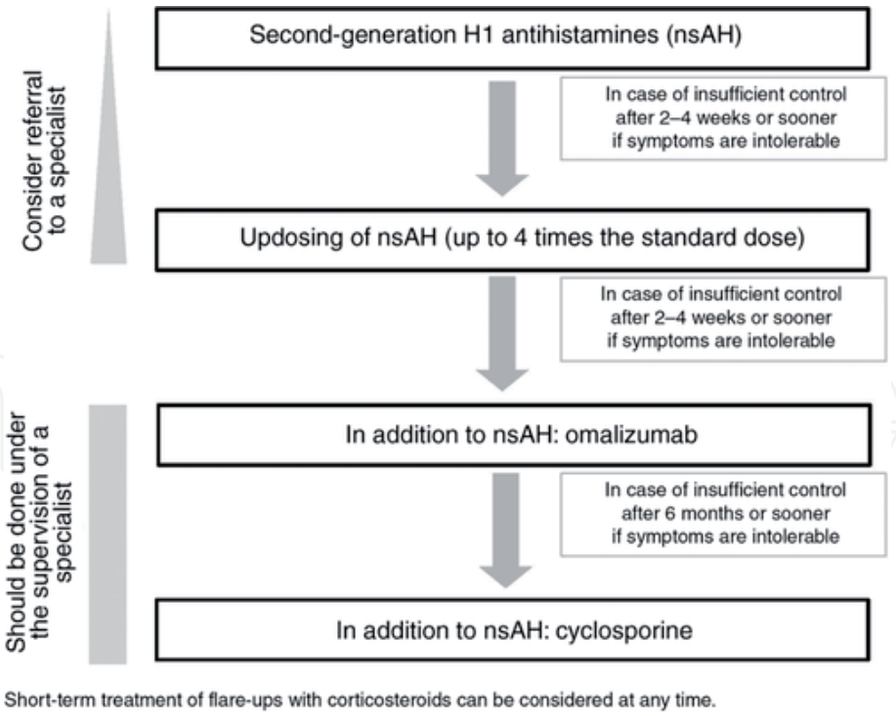


Figure 19.
Recommended treatment algorithm for chronic urticaria.

Not included in algorithm H2 antihistamines (used only on an individual case).

Avoid first-generation H1 antihistamines based on benefit to risk ratio.

Corticosteroids may be considered only for the short-term intervention.

Cyclosporine A for refractory chronic urticaria not responsive to other treatments.

*Cyclosporin A is an immunosuppressive agent, widely used in organ transplantation to prevent rejection.

The current version of the *EAACI/GA²LEN/EDF/WAO urticaria guideline* recommends:

When chronic inducible urticaria is suspected, differential diagnoses should be ruled out. The diagnosis should be confirmed by provocation test disease. The activity should be measured by determining the trigger threshold disease burden and control should be measured.

Second-generation H1 antihistamines remain the treatment of first choice.

If continuous treatment for 2–4 weeks does not lead to adequate control of symptoms, the guidelines recommend up-dosing (up to four times the standard dose).

If there is no improvement with high-dose antihistamines, it is recommended to add omalizumab to the regimen in patients with chronic spontaneous urticaria.

If there is no success after 6 months of omalizumab therapy, off-label treatment with cyclosporine is recommended.

7. Assessment scales

Assessment scales serve to evaluate the treatment, as well as this pathological entity affects the quality of life of the patient. We have the urticarial activity score (UAS) [15] or angioedema activity score (AAS) [16], chronic urticaria quality-of-life questionnaire, and urticaria control test (UCT).

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 h)	Mild (present but not annoying or troublesome)
2	Moderate(20-50 wheals/24 h)	Moderate (troublesome but does not interfere with normal daily activity or sleep
3	Intense (>50 wheals/24 h or large confluent areas of wheals)	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)

Sum of score: 0–6.

Figure 20.
UAS.

Urticaria control test

Name: _____ Date: ____ . ____ . _____

Date of birth: _____ . ____ . _____

Instructions: You have hives (urticaria). The following questions are meant to assess the current disease status. Please read each question carefully and select the one answer that *best describes your situation.* Please refer to the *past 4 weeks. Don't ponder for too long and remember to answer all questions* and to select *only one answer* for each question.

1. To what extent have you suffered from **physical symptoms of urticaria (pruritus, wheals and/or swelling)** in the past 4 weeks?
   O very severely O severely O moderately O slightly O not at all
2. How much has your **quality of life** been affected by the urticaria in the past 4 weeks?
   O very severely O severely O moderately O slightly O not at all
3. How often has the **treatment** of your urticaria **not been sufficient** to control the urticaria symptoms in the past 4 weeks?
   O very frequently O frequently O occasionally O rarely O not at all
4. How well has your urticaria been **under control overall** in the past 4 weeks?
   O not at all O hardly O moderately O well O completely

Figure 21.
Urticaria control test.

The current guideline endorses the urticaria activity score and/or the angioedema activity score to assess the disease activity in CSU patients [17] (**Figure 20**).

The urticaria control test should be used in all CSU patients. The UCT is a retrospective tool used to rapidly and reliably assess disease control with four simple questions (**Figure 21**). Patients answer each of the four UCT questions, and the corresponding points (0–4 per answer) are added up to yield a total score of 0–16. The cutoff for controlled urticaria is 12 points. A score of 11 or less indicates insufficient disease control, whereas a score of 12 or more suggests adequate disease control [18].

Conflict of interest

None.

Thanks

We want to thank IntechOpen for the opportunity to publish this chapter. We also want to thank our friends and family for their patience and unconditional support.

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