ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

An update on the Brazilian Association of Allergy and Immunology Practical Guide for the Diagnosis and Management of Urticaria based on the international guideline

Atualização do Guia Prático da Associação Brasileira de Alergia e Imunologia para o Diagnóstico e Tratamento da Urticária baseado na diretriz internacional

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ABSTRACT

Urticaria is a condition characterized by the presence of hives, angioedema, or both. It can be classified according to its duration as acute, when it persists for less than 6 weeks, or chronic, when it persists for more than 6 weeks and greatly affects quality of life. Updated recommendations on diagnosis and management are developed by experts from all over the world who meet every 4 years in Berlin and review all new evidence that supports changes to the international guideline. This paper discusses the main recommendations proposed in the current version of the international guideline.

Keywords: Urticaria, angioedema, diagnosis, evidence-based practice.

RESUMO

A urticária é uma condição caracterizada pela presença de urticas, angioedema, ou ambos, que pode ser classificada de acordo com o tempo de duração em aguda, quando persiste por menos de 6 semanas, ou crônica, quando por mais de 6 semanas e afeta significativamente a qualidade de vida. A atualização das recomendações quanto ao seu diagnóstico e tratamento é elaborada por especialistas de todo o mundo, que se reúnem a cada quatro anos em Berlim para revisar todas as novas evidências que justifiquem modificações na diretriz internacional. Este artigo discute as principais recomendações propostas na versão atual da diretriz internacional.

Descritores: Urticária, angioedema, diagnóstico, prática clínica baseada em evidências.

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Introduction

The purpose of this guide is to provide a practical discussion of the main recommendations from the current version of the International Guideline for the Definition, Classification, Diagnosis, and Management of Urticaria. The update and revision of the international guideline was conducted according to the methods recommended by Cochrane and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group. The conference took place in a hybrid format, both in Berlin and online, on December 3, 2020. The updated version was acknowledged and accepted by the European Union of Medical Specialists (UEMS) and published in early 2022. It was a joint initiative of the Dermatology Section of the European Academy of Allergy and Clinical Immunology (EAACI), the Global Allergy and Asthma European Network (GA²LEN) and its Urticaria and Angioedema Centers of Reference and Excellence (UCAREs and ACAREs), the European Dermatology Forum (EDF), and the Asia-Pacific Association of Allergy, Asthma, and Clinical Immunology (APAAACI) with the participation of 64 delegates of 50 national and international societies and from 31 countries.[1,2]

The updated guideline covers the definition and classification of urticaria and outlines expert-guided and evidence-based diagnostic and therapeutic approaches for the different subtypes of urticaria.

Definition

Urticaria is a common and heterogeneous inflammatory skin condition characterized by the appearance of wheals—edematous lesions of variable size, usually surrounded by erythema, itchy and fleeting in nature, and typically lasting ≤ 24 hours without leaving residual marks[1,3] (Figure 1). Angioedema, in contrast, manifests as sudden and pronounced swelling in the lower dermis and subcutis or mucous membranes, often accompanied by pain, burning, or itching. Angioedema has a slower resolution than that of wheals, sometimes lasting up to 72 hours (Figure 2).[1]

Classification

Urticaria is classified based on its duration as either acute or chronic and by the role of specific triggers as spontaneous or inducible. Acute urticaria

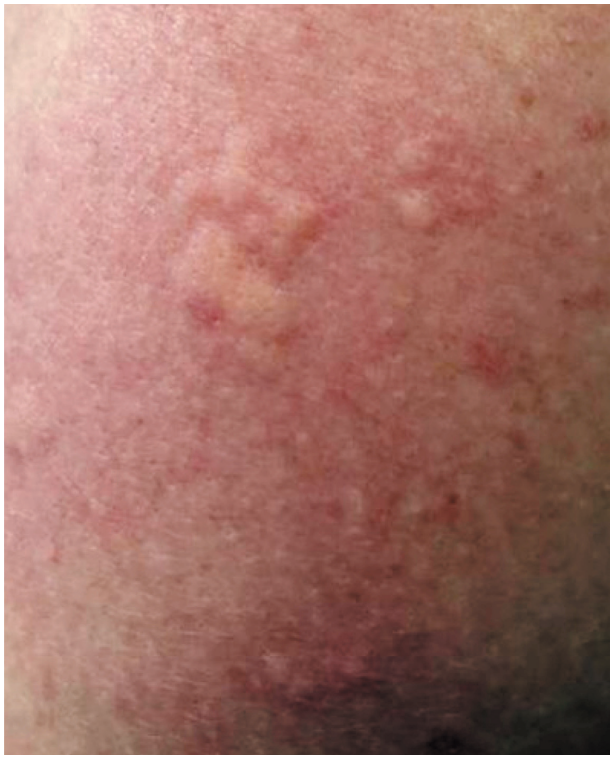


Figure 1
Wheals
Source: Personal archive of R. Agondi.

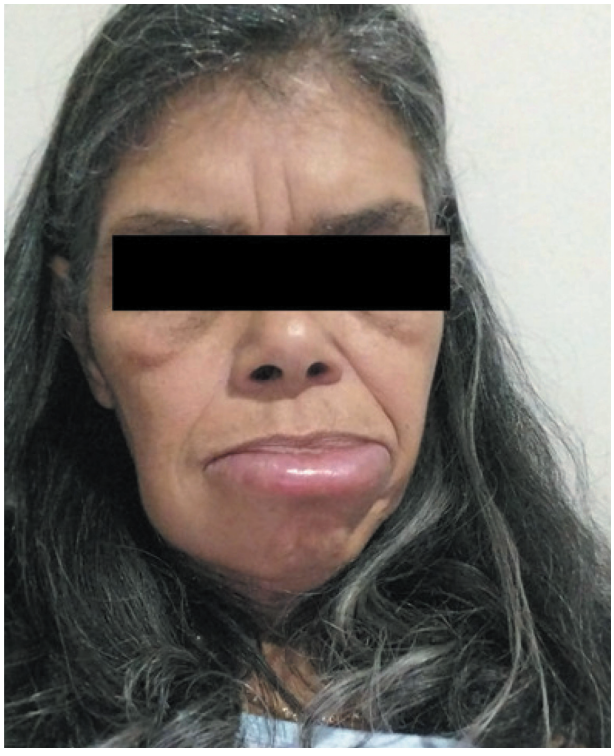


Figure 2
Angioedema
Source: Personal archive of G. Dias.

(AU) is defined as the appearance of wheals and/or angioedema for 6 weeks or less. Chronic urticaria (CU) is defined as the occurrence of wheals and/or angioedema for more than 6 weeks. Symptoms in CU may occur daily, almost daily, or with an intermittent or recurring course.[1]

CU may occur spontaneously, referred to as chronic spontaneous urticaria (CSU), or as a result of specific triggers, known as inducible chronic urticaria (CIndU). CIndU is further subclassified into symptomatic dermographism, cold urticaria, heat urticaria, delayed pressure urticaria, solar urticaria, vibratory angioedema, cholinergic urticaria, aquagenic urticaria, and contact urticaria (Table 1).[1,3] Patients can have more than one type of CU simultaneously.[3]

Epidemiology and natural course

Urticaria is a common condition resulting from mast cell activation, presenting with wheals, angioedema, or both. The lifetime prevalence of AU is approximately 20%. CU, whether spontaneous or inducible, is debilitating, significantly impairs quality of life, and affects performance at work and school. The prevalence of CU ranges from 0.1% to 1.0%, with a recent study reporting a prevalence of diagnosed CU of 0.41% in the Brazilian population.[4]

The average duration of AU is 1 week, with the rate of progression from acute to chronic varying from 5% to 39% across most studies. CU typically lasts between 1 and 4 years, with spontaneous remission occurring in approximately 45% of cases after 5 years of disease. In patients followed at a urticaria referral and excellence center in Brazil, the median duration of CU was 24 months at the time of diagnosis, while those who entered remission had a median duration of 72 months at discharge.[5] Another Brazilian center reported an average duration of 10.2 years in patients undergoing follow-up.[6]

Recurrence of urticaria symptoms occurs in about one-third of patients. CIndU generally has a longer duration than CSU, which varies according to each subtype.[3]

Table 1
Classification of chronic urticaria[1]

Chronic spontaneous urticaria	Chronic inducible urticaria
Spontaneous appearance of wheals and/or angioedema	Symptomatic dermographism
for > 6 weeks	Cold urticaria
Without a specific trigger	Heat urticaria
	Solar urticaria
	Delayed pressure urticaria
	Vibratory angioedema
	Aquagenic urticaria
	Cholinergic urticaria
	Contact urticaria

Pathophysiological aspects

Mast cells play a central role in urticaria. Histamine and other mediators, such as cytokines released from activated skin mast cells, lead to sensory nerve activation, vasodilatation, and plasma extravasation, as well as cell recruitment (T lymphocytes, eosinophils, and neutrophils) to lesions. The mast cell-activating stimuli in urticaria are heterogeneous and include, for example, T cell-driven cytokines and autoantibodies. Histologically, wheals are characterized by edema of the upper and mid dermis, with dilatation and augmented permeability of the postcapillary venules of the upper dermis.[1,3]

Type I hypersensitivity reactions are primarily associated with AU and occur due to specific interactions between IgE antibodies, which are bound to the surface of mast cells, and specific allergens, leading to mast-cell activation. Medications, foods, and insect venom are major causes of this type of reaction.[3]

Although the pathogenesis of CU is not fully understood, two pathogenic mechanisms have been proposed for mast-cell activation in CSU, both involving autoimmune processes. The first mechanism is known as autoimmune CSU or type IIb autoimmunity (CSU^{aiTIIb}), associated with immunoglobulin (Ig) G autoantibodies to FcεRI (IgG anti-FcεRI) or IgG anti-IgE. The second proposed autoimmune mechanism is termed autoallergic CSU or type I autoimmunity (CSU^{aiTI}) and involves IgE antibodies to autoantigens. The most studied and recognized autoantigens in this context are thyroid peroxidase (IgE anti-TPO) and interleukin-24 (IgE anti-IL-24)[1,3] (Figure 3).

Diagnosis of urticaria

Diagnosis of acute urticaria

AU does not typically require additional workup (Table 2). In most cases, it is associated with viral infections (especially in children), but may also

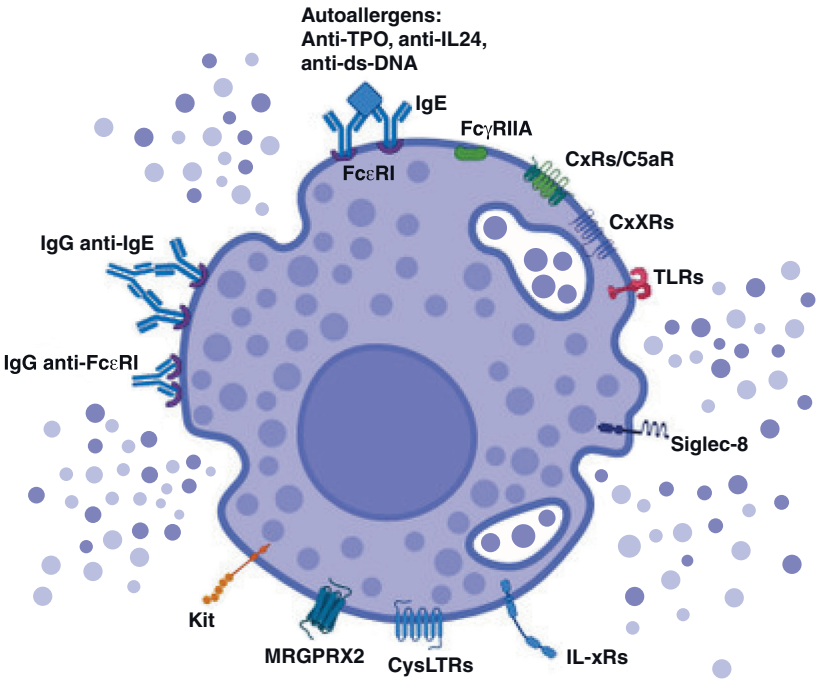


Figure 3
Mechanisms of type I and type IIb autoimmunity
Several receptors that induce mast cell degranulation are illustrated.[7,8]

CxRs = complement receptors, CxXrs = chemokine receptors, CysLTRs = cysteinyl leukotriene receptors, FcεRI = IgE receptor-I, FcγRIIA = IgG receptor-IIA, IL-xRs = interleukin receptors, MRGPRX2 = MAS-related G protein-coupled X2 receptor, Siglec-8 = sialic acid-binding immunoglobulin-like lectin-8, TLRs = Toll-like receptors, TPO = thyroperoxidase.

Table 2
Recommended diagnostic tests in the investigation of urticaria

Type	Subtype	Recommended routine diagnostic tests	Extended diagnostic program[a]
Spontaneous urticaria	Acute spontaneous urticaria	None	None[b]
	Chronic spontaneous urticaria	Differential blood count, ESR and/or CRP, IgG anti-TPO, and total IgE[c]	Identify suspected triggers (eg, medications); diagnostic tests for 1) infectious diseases, 2) functional autoantibodies (eg, basophil test), 3) thyroid disorders (thyroid hormones and autoantibodies), 4) skin allergy tests and/or allergen avoidance test, 5) concomitant CIndU, 6) systemic disease.
Inducible urticaria	Cold urticaria	Ice cube provocation test and/or TempTest 4.0® [d,e]	Differential blood count, ESR or CRP, and rule out differential diagnoses, especially infections
	Delayed pressure urticaria	Dermographometer/ Warin test [d,e]	None
	Heat urticaria	Heat provocation test and TempTest 4.0® [d,e]	None
	Solar urticaria	Provocation test with U-V and visible light of different wavelengths [d,e]	Rule out other light-induced dermatoses
	Symptomatic dermographism	Fric-test® 4.0/ dermographometer [d,e]	Differential blood count, ESR or CRP
	Vibratory angioedema	Provocation test with a vortex-mixer [d,e]	None
	Aquagenic urticaria	Provocation test with a water compress [d,e]	None
	Cholinergic urticaria	Ergometry provocation test [d,e]	None
	Contact urticaria	Open provocation test with the suspected allergen [d,e]	None

CIndU = chronic inducible urticaria, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, Ig = immunoglobulin, TPO = thyroid peroxidase.
[a] Depending on the suspected cause.
[b] Unless strongly suggested by patient history, for example, allergy.
[c] For patients in specialist care.
[d] All tests are performed with different levels of the potential trigger to determine the threshold.
[e] For details on the provocation test, refer to CIndU.

occur spontaneously without any identifiable trigger (idiopathic).[9] Exceptions occur in the suspicion of AU in association with IgE-mediated allergies. In these cases, allergy skin tests or serum-specific IgE measurements should be considered. In our population, foods, medications, and Hymenoptera insect venom are major causes of IgE-mediated urticaria.[10]

Analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) are common causes of AU through non-IgE-mediated mechanisms. NSAID-induced urticaria often presents with angioedema alone, without wheals. Thorough investigation of these cases is crucial to ensure that the patient receives adequate guidance and to avoid further reactions.[11,12]

Extra caution is needed in cases of medication-induced urticaria to avoid misdiagnosing a patient as allergic to a particular medication without adequate investigation.[11,13]

Diagnosis of chronic spontaneous urticaria

The cornerstones of CSU diagnosis are a thorough clinical history and a physical examination showing evidence of wheals and/or angioedema. However, basic laboratory tests may also be performed, including differential blood count, C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR), and total IgE and IgG anti-TPO for all patients with CSU. These tests are important to rule out other conditions associated with urticaria, such as chronic infections, lymphoproliferative diseases, autoimmune disorders, and autoinflammatory diseases.[1] In addition, CRP is a useful marker for assessing urticaria activity, as elevated CRP levels may be directly linked to more severe cases of urticaria.[14] Total IgE and IgG anti-TPO levels are useful for evaluating the autoimmune endotype and treatment response. Although extensive laboratory investigation is not typically recommended, additional tests may be necessary depending on the patient's clinical history, physical examination, and routine diagnostic test results (Table 2).[1]

In CSU, diagnostic evaluation should focus on seven key objectives (referred to as the "7 Cs"): confirm the diagnosis and exclude differential diagnoses; look for the underlying causes; identify cofactors, that is, relevant conditions that modify disease activity; check for comorbidities; identify the consequences of CSU; assess predictors of the course of disease and response to treatment; and monitor disease control, activity, and impact (Table 3).[1,15]

Identification of underlying causes and factors

Determining the underlying cause of CSU remains uncertain and challenging. Based on recent evidence, the main hypotheses for CSU pathogenesis include autoimmunity (CSU^{aiTI} and CSU^{aiTIIb}) and, in some cases, unknown mechanisms that play a role in skin mast cell degranulation.[15,16]

History and physical examination may provide clues about the underlying cause, and basic laboratory test results may be indicative of CSU^{aiTI} or CSU^{aiTIIb}. Elevated CRP levels and low eosinophil and basophil counts are indicative of probable CSU^{aiTIIb}. Measurement of total IgE and IgG anti-TPO levels should be included in the evaluation of patients with CSU, as those with CSU^{aiTIIb} are more likely to have low total IgE and elevated IgG anti-TPO.[1,16]

A positive basophil activation test (BAT) may also be indicative of CSU^{aiTIIb}, with a positive predictive value for diagnosis of 69%.[1,17,18] However, the BAT is not commonly used in medical practice, as it is not widely accessible in most Brazilian urticaria reference centers.

Knowing the relevant conditions that can modify disease activity and factors that exacerbate CSU helps both physicians and patients better manage the disease. Therefore, during each consultation, patients should be asked about factors that exacerbate their CSU.

Medications can worsen CSU in about one-third of patients. NSAIDs are the most common triggers, except for selective and preferential COX-2 inhibitors and/or acetaminophen, which are considered safer options for patients with CSU. When indicated, patients should be advised to avoid NSAIDs to prevent exacerbations.[1,19,20]

Certain foods may also exacerbate CSU by acting as "pseudoallergens." These low-molecular-weight compounds may bind to MRGPRX2 receptors on the surface of mast cells, triggering their activation and the release of mediators.[21] Based on patient response, a diet low on these "pseudoallergens" or avoidance of histamine-rich foods, such as fish, seafood, fermented foods (bacon, cheese), and some vegetables (spinach, eggplant, tomatoes), may be considered as an individualized diagnostic and therapeutic measure. However, it should be noted that these diets remain controversial and should not be routinely recommended, as they may further reduce the already compromised quality of life of patients with CSU. If a food is suspected to worsen CSU, an

Table 3
Objectives of diagnostic workup in patients with CSU

Patients with CSU – What should we assess?			
	Clinical history	**Physical examination[a]**	**Basic tests[b]**
Confirm	Rule out differential diagnoses.		
Cause	Check for indicators of type I (autoallergic) or type IIb (autoimmune) CSU.		
Cofactors	Identify potential triggers or aggravators.		
Comorbidities	Check for concomitant CIndU, autoimmunity, and mental health.		
Consequences	Identify problems with sleep, activities of daily living, sexual life, and social performance.		
Course	Monitor CSU activity (UAS), control (UCT), and impact (CU-Q2oL).		
Components	Evaluate potential biomarkers or predictors of treatment response.		

[a] Including review of patient photo documentation.
[b] Differential blood count, ESR/CRP rate, total IgE, and IgG anti-TPO.

CIndU = chronic inducible urticaria, CSU = chronic spontaneous urticaria, CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire, ESR/CRP = erythrocyte sedimentation/C-reactive protein, Ig = immunoglobulin, TPO = thyroid peroxidase, UAS = Urticaria Activity Score, UCT = Urticaria Control Test.

exclusion diet for 3-4 weeks is recommended for diagnostic purposes.[1,15,22]

Stress may worsen skin symptoms in about one-third of patients with CSU. Stress-related neuropeptides can activate mast cells through the MRGPRX2 receptor.[21] Patients should be assessed for the impact of stress on their condition and informed that stress reduction may be a useful strategy for controlling urticaria.[1,19]

Acute viral and chronic bacterial infections may exacerbate CSU and modify disease activity. However, evidence suggests that chronic viral infections, such as hepatitis B or C, do not modulate CSU activity. Therefore, routine screening for chronic viral infections is not recommended. Regarding chronic bacterial infections, studies on *Helicobacter pylori* have shown mixed and contradictory results. The effect of *H. pylori* eradication on the course of CSU remains controversial, and *H. pylori* infection should be investigated based on clinical history. The role of fungal infections in CSU is still poorly understood, and more studies are needed to better define their prevalence and relevance.[19]

Identification of comorbidities and consequences of CSU

In CSU, the most common comorbidities include CIndUs, autoimmune diseases (especially autoimmune thyroid disease), and atopy. Mental disorders such as depression, anxiety, sexual dysfunction, and sleep disturbances are also frequent. Findings from the patient's clinical history, physical examination, and basic laboratory tests that indicate a comorbidity should always be evaluated.[19]

Identification of predictors for disease course and

treatment response

Currently, there are no definitive predictors of disease duration, activity, and treatment response in CSU.[19] However, these variables are often linked to clinical characteristics and laboratory markers, which can help physicians to guide patients about the severity and expected duration of their disease and treatment response. For example, concomitant CIndU, severe disease activity (elevated CRP and D-dimer levels), and/or angioedema indicate a longer duration of CSU and poorer response to antihistamines. Conversely, low IgE levels are associated with a reduced response to omalizumab, while a positive BAT and low IgE levels may suggest a better response to cyclosporine.[14] However, it should be noted that low total IgE levels are not a contraindication to treatment with omalizumab.

Diagnosis of inducible urticarias

CIndUs include both physical and nonphysical urticarias. CIndUs may be diagnosed through clinical history, physical examination, and provocation tests[23] (Table 2).

Symptomatic dermographism (or dermographic urticaria)

Symptomatic dermographism is characterized by the appearance of linear and itchy wheals due to shearing forces on the skin, which may result from friction, scratching, or rubbing. It is rarely associated with angioedema.

It is the most common CIndU, affecting 2% to 5% of the general population and accounting for 30% to 50% of CIndU cases, in addition to being frequently associated with CSU. The diagnosis of symptomatic dermographism is confirmed by applying a stroking pressure to the skin with a blunt object, such as a spatula or the blunt end of a pen. Standardized tests such as the Fric Test® or dermographometers are preferred. The test is considered positive when an itchy wheal appears at the test site within 10 minutes of provocation.[23]

Delayed pressure urticaria (DPU)

Patients with DPU develop wheals and/or angioedema 4 to 6 hours after the application of a sustained pressure to the skin. Lesions may appear within 4 to 12-24 hours and may last up to 72 hours. Provocation tests for DPU include:

- Suspension of weights (7 kg on a 3-cm shoulder strap) on the patient's shoulder for 10 to 15 minutes.
- The Warin test, which involves the use of a 15-cm diameter sphere to exert localized pressure on the outer aspect of the forearm beneath a cuff to which is attached a bag containing 4-kg worth of materials, for 5 minutes.
- Application of weighted rods lowered vertically onto the skin and supported in a frame on the back, high, or forearms.
- The use of a dermographometer, applied perpendicularly at 100 g/mm² (981 kPa) for 70 seconds on the upper back (directly beneath the scapula).

The tests are considered positive when wheals and/or angioedema appear at the test site 4-6 hours after provocation.[23]

Cold urticaria

Cold urticaria is characterized by the appearance of wheals after contact with cold objects, air, or liquids. Cold provocation tests include the traditional ice cube test and the TempTest®.[2,4]

- The ice cube test involves applying a melting ice cube contained within a plastic bag on the patient's forearm for 5 minutes. Test response should be assessed 10 minutes after the end of the test and is considered positive if the test site shows the appearance of a wheal.
- The TempTest® is a validated device for the diagnosis of cold and heat urticaria by measuring temperature thresholds and disease activity. The patient's forearm is placed on the TempTest® temperature element for 5 minutes. The test is considered positive if a 2-mm wide wheal (width of the TempTest® element) appears 10 minutes after the start of the provocation test.[23]

Heat urticaria

Heat urticaria is a rare form of CIndU characterized by the appearance of wheals immediately after contact heating of the skin. Diagnosis is confirmed by applying a hot stimulus (eg, a metal/glass sphere filled with hot water or hot water baths of up to 44°C) to the skin of the volar forearm for 5 minutes. Test response should be assessed after 10 minutes. Alternatively, the TempTest® may be used.[23]

Solar urticaria

Patients with solar urticaria develop wheals within minutes of skin exposure to sunlight (UV-A [320-400 nm wavelength] or visible light [400-600 nm wavelengths]). Less frequently, lesions may also be triggered by UV-B (280-320 nm) or infrared radiation (> 600 nm). Provocation tests include:

– A slide projector (for visible light).
– Black fluorescent light (UV-B and UV-A).
– Fluorescent sunlight lamp (UV-B and UV-A).
– Infrared lamp (infrared range).

The minimum erythema dose (MED) of urticaria is determined by exposing a 1 cm^2 area of skin to a light source from 10 cm away and reading the result after 10 minutes.[23]

Vibratory angioedema/urticaria

Patients with vibratory angioedema/urticaria present with itching and wheals within minutes of skin exposure to vibration.

Provocation test for diagnosis may be performed using a laboratory vortex mixer. The patient's forearm is held on a plastic plate laid on the vortex mixer that is continuously run between 780 rpm and 1380 rpm for 5 minutes. Test response should be assessed after 10 minutes.[23]

Aquagenic urticaria

Aquagenic urticaria is a rare form triggered by contact with water, regardless of its temperature. The diagnosis is confirmed by applying a compress or a towel soaked with 35-37 °C water or physiological saline to the patient's trunk. The compress or the towel should be removed after 40 minutes or earlier, if the patient reports itching or if wheals appear at the test site. The test is positive if the lesions develop within the contact area up to 10 minutes after the compress/towel is removed.[23]

Cholinergic urticaria

Cholinergic urticaria is characterized by the appearance of punctiform wheals due to increased body temperature from exercise, local heat application, emotional stress, spicy foods, or hot drinks.

In addition to diagnostic purposes, provocation test in cholinergic urticaria also has the goal of ruling out exercise-induced anaphylaxis. The diagnosis is confirmed when the patient's core temperature increases by more than 1 °C from baseline after passive warming in a hot water bath (≤ 15 min at 42°C).

A standardized protocol using ergometry with heart rate monitoring has been proposed to diagnose and measure the thresholds for cholinergic urticaria. The patient is seated on a bicycle ergometer and instructed to cycle until an increase in heart rate of 15 beats per minute (bpm) every 5 minutes is achieved until it reaches 90 bpm above baseline after 30 minutes. Time to whealing is correlated with disease severity—faster onset means more severe cholinergic urticaria.[23,24]

Differential diagnosis of urticaria

Wheals or angioedema can also occur in conditions other than AU and CSU (Table 4).

A key aspect in the differential diagnosis of wheals/angioedema is their appearance. Unlike the wheals associated with AU or CU, other urticarial-like lesions may be more hardened, discolored, or darkened, last longer than 24 hours in most cases, and resolve with residual marks, typically hyperpigmentation. These lesions often cause pain or burning, with little or no itching, and angioedema is typically absent. Systemic symptoms such as arthralgia, fever, malaise, and weight loss may be associated and should be further investigated.[25]

Isolated, recurrent angioedema evokes multiple differential diagnoses, and warning signs include the absence of response to H1 antihistamines, corticosteroids, and epinephrine (suggesting a bradykinin-mediated mechanism); the presence of similar cases in other family members (hereditary angioedema); and the presence of other symptoms or diseases, particularly lymphoproliferative disorders and collagen diseases (acquired angioedema). Association with medication use should always be considered in cases of isolated recurrent angioedema, especially with angiotensin-converting enzyme inhibitors (bradykinin-mediated mechanism) and NSAIDs (histamine-mediated mechanism). Table 5 lists the main diagnoses to be considered in cases of isolated recurrent angioedema.[26]

Other conditions that may involve edema and should be considered in the differential diagnosis of angioedema include infections (cellulitis), Melkersson-Rosenthal syndrome, contact dermatitis, thyroid diseases, and dermatomyositis.[26]

Table 4
Differential diagnoses of urticarial lesions[25-28]

Condition	Pathophysiology	Secondary associations	Indicative features	Investigation
Cutaneous mastocytosis	Genetic	Systemic mastocytosis	Darier's sign may be present	Skin biopsy for mast cell infiltrate. Serum for c-KIT D816V analysis
Erythema multiforme	Hypersensitivity	Infections and drugs (less common)	Target lesion with a central dusky area	Inflammatory markers PCR for HSV or mycoplasma. Skin biopsy for keratinocyte necrosis
Urticarial vasculitis	Inflammatory	Autoimmune diseases. Lymphoproliferative diseases. Infections. Drugs	Bruised lesions that heal with ecchymotic hyperpigmented marks	Inflammatory markers. Serum complements. Screening for autoimmune, infectious, and lymphoproliferative diseases. Skin biopsy for leukocytoclastic vasculitis and neutrophilic predominance
Erythema marginatum	Genetic	Hereditary angioedema	Often manifests as a prodrome of angioedema exacerbation	Serum C4 Serum C1 esterase inhibitor (qualitative and quantitative). Genetic study for patients with normal C1 inhibitor (*F12* variants, others)
Urticarial dermatitis	Inflammatory	None	Pruritic, erythematous plaques and papules lasting longer than 24 hours	Skin biopsy for dermal edema and spongiosis or minimal lichenoid reaction
Bullous pemphigoid	Autoimmune	None	Tense blisters form on the urticarial base	Direct immunofluorescence for linear IgG deposition along the basement membrane. Indirect immunofluorescence for IgG deposition along the basement membrane
Polymorphic eruption of pregnancy	Inflammatory	None	Small itchy papules and plaques start in stretch marks and spread to the periumbilical area	Clinical diagnosis, no tests needed.
Autoinflammatory syndromes	Genetic	Amyloidosis	Urticarial rash lasting > 24 hours accompanied by systemic inflammation (recurrent fever, joint pain, weight loss, etc.) dor articular, perda de peso, etc.)	Nonspecific skin biopsy, predominance of neutrophilic urticaria. Consider genetic evaluation in children. Laboratory tests according to the suspected syndrom

HSV = herpes simplex virus, IgG = immunoglobulin G, PCR = polymerase chain reaction.

Assessment of urticaria activity, impact, and control

An accurate assessment of clinical status, disease activity, and progression is crucial for the adequate understanding and management of CU to help reduce its impact on several domains of patients' lives and improve their overall well-being. Therefore, in 2011, the GA²LEN recommended the use of the Patient Report Outcomes Measures (PROMs) for the assessment of CU in daily clinical practice and as a primary outcome in clinical studies.[29] It is recommended that patients be evaluated regarding disease activity, impact, and control during each medical visit.[30]

CU severely compromises the quality of life of patients due to its unpredictable, debilitating, and uncomfortable symptoms, which can persist for years.[31]

Currently, there are insufficient data to validate the use of laboratory biomarkers alone to identify and measure disease activity. Thus, the use of PROMs is critical in the assessment and monitoring of patients, as well as to provide objective data to help guide decision-making on the best treatment option.[29,31,32]

There are six instruments used to assess CU, namely: Urticaria Activity Score summed over 7 days (UAS7), Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL), Urticaria Control Test (UCT), Angioedema Activity Score (AAS), Angioedema Quality of Life Questionnaire (AE-QoL), and Angioedema Control Test (AECT). These instruments are either validated or in the process of being validated for use in Brazilian Portuguese (Table 6).[33-38]

The main tool for assessing urticaria activity is the UAS7, a questionnaire based on the prospective evaluation by patients of their symptoms (itching and wheals) over 7 consecutive days. The total score is the sum of the 7 days, and it ranges from 0 to 42. The UAS7 allows the categorization of disease severity as follows: 0 = urticaria-free; 1-6 = well-controlled urticaria; 7-15 = mild urticaria; 16-27 = moderate urticaria; and 28-42 = severe urticaria.[33] A UAS7 score of ≤ 6 is considered adequate, but it should be preferably close to 0, which is the treatment target for patients with CSU.[1]

Although the UAS7 has proven to be a useful tool and has become the gold standard for measuring disease activity in patients with CSU, it has some limitations: it does not account for angioedema, does not evaluate CIndU, and does not assess disease control. In addition, it relies on the patient's commitment to correctly fill in the information.[32]

The UCT was specifically developed to assess CU control status, addressing the limitations of the UAS7. It is a retrospective questionnaire that evaluates urticaria control based on patient perception over the previous 4 weeks. The total score ranges from 0 to 16, with higher scores indicating better control, and has a cut-off point of 12, meaning that a score of 12 or higher indicates that the disease is under control.[31] The UCT assesses both CSU and CIndU and also takes into account angioedema. It is easy to use in clinical practice and can be administered during routine medical visits.[35,39]

The CU-Q2oL is another tool that effectively measures the impact of CU on quality of life. The questionnaire consists of 23 questions regarding the 2 weeks prior to the consultation. Each question has five response options, ranging from 1 (not at all) to 5 (very much), with a total score ranging from 23 to 115, where a higher score indicates a worse quality of life. The CU-Q2oL has been validated in Brazilian Portuguese.[34,40] Some limitations include that it only evaluates CSU and not CIndU, is validated only for adults, lacks severity categorization, and does not include specific questions about the impact of angioedema.[32]

The AAS is a simple tool that can determine disease activity in patients with recurrent angioedema. It consists of 5 questions about the occurrence of angioedema in the last 24 hours that patients should complete daily. The questions cover symptom duration, main complaints, limitations in activities of daily living, effects on physical appearance, and symptom severity, in addition to indirectly assessing the interval between episodes. The score ranges from 0 to 3 for each question, with a maximum total score of 15, which reflects severe angioedema activity.[41]

Patients should complete the AAS for at least 28 days because angioedema may be more episodic than urticaria. Patients with CSU who present with both wheals and angioedema should be instructed on the differences between these lesions, as errors in evaluation may lead to an inaccurate assessment of angioedema activity.[41]

The AE-QoL is the first validated tool to measure the impact of recurrent angioedema on quality of life. It includes 17 questions, each with 5 response options ranging from 1 (never) to 5 (very frequently), with a total score ranging from 17 to 85. A higher score indicates greater impairment in health-related quality of life. The questionnaire was validated in Brazilian Portuguese.[36,37] The main limitations of the AE-QoL

include its length, which can hinder its use in daily practice; it only provides information on angioedema and should be complemented by urticaria-specific tools; and patients may confuse angioedema with wheals, compromising the assessment.[32]

The AECT is the first tool developed to assess disease control in patients with any type of recurrent angioedema. It consists of 4 questions related to the frequency of symptoms, quality of life, disease unpredictability, and treatment, with a score ranging from 0 to 16. A score of 16 represents total control, while a score of ≥ 10 and < 10 indicates good control and lack of control, respectively. Because the AECT was only recently developed, it is currently in the process of being validated in Brazil.[38]

Treatment

Treatment goals

The main goal of CU treatment is to achieve complete control of symptoms whenever possible, allowing patients to enjoy the best possible quality of life and perform activities of daily living without impairment or limitations.[1] The treatment should follow

Table 5
Nonhistaminergic recurrent angioedema[26]

Condition	Pathophysiology	Secondary associations	Indicative features	Investigation
Hereditary angioedema	Genetic	Erythema marginatum	Family history	Serum C1 esterase inhibitor (qualitative and quantitative). Serum C4. Genetic study for patients with normal C1 inhibitor (*F12* variants, others)
Acquired angioedema	Complement consumption	Lymphoproliferative disorders. Solid tumors. Autoimmune. Medications: ACE inhibitors	Angioedema unresponsive to conventional treatment. Associated systemic symptoms	Serum C1 esterase inhibitor (qualitative and quantitative). Serum C4. Serum C1q
Eosinophilic angioedema (Gleich syndrome)	Interleukin-5	Hypereosinophilic syndrome	Weight gain, significant eosinophilia, unilateral facial edema involving the neck, and painful limb edema	Skin biopsy showing eosinophilic infiltrate. ESR, CRP, LDH, serum albumin, C3, and C4

ACE = angiotensin-converting enzyme, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, LDH = lactate dehydrogenase.

Table 6
Instruments for urticaria assessment

	CSU		
Clinical presentation	Wheals	Wheals and angioedema	Angioedema
Disease activity	UAS7	UAS7 and AAS	ASA
Disease control	UCT	UCT and AECT	AECT
Quality of life	CU-Q2oL	CU-Q2oL and AE-Q2oL	AE-Q2oL

AAS = Angioedema Activity Score, AECT = Angioedema Control Test, AE-Q2oL = Angioedema Quality of Life Questionnaire, CSU = chronic spontaneous urticaria, CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire, UAS7 = Urticaria Activity Score summed over 7 days, UCT = Urticaria Control Test.

the basic principles of "treating as much as needed and as little as possible," as long as symptoms remain under control. Urticaria is considered controlled when the UCT score is ≥ 12 and/or the UAS7 is ≤ 6, while a UCT score of 16 and a USAS7 score of 0 means absence of symptoms.[42] Once disease control is achieved, reduction of treatment should be considered to reduce the therapeutic burden and to assess spontaneous remission. Treatment should continue until urticaria is in complete remission, and regular patient reassessment is important (Figure 4).

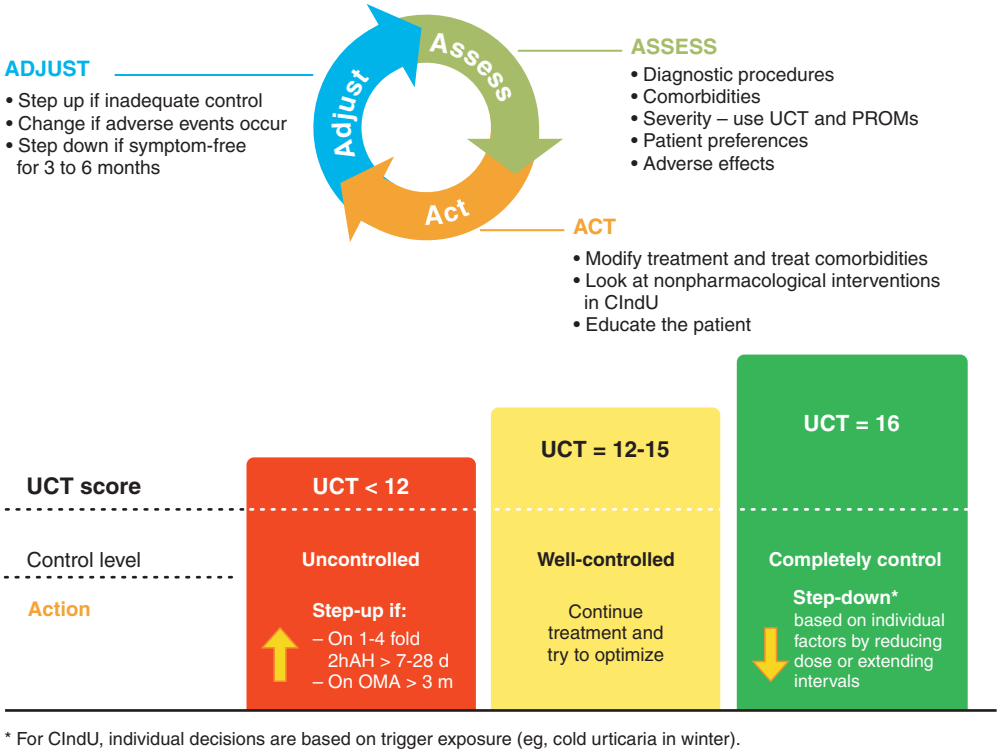
First-line treatment: second-generation nonsedating antihistamines

Second generation nonsedating antihistamines are recommended as first-line treatment for all types of urticaria. Updosing up to a fourfold is recommended in patients with urticaria refractory to a standard dose.

Second-generation H1-antihistamines are the first-line treatment for both AU and CU, with an excellent safety profile across all age groups, causing minimal to no sedation and free from anticholinergic effects.[43,44]

Compared to first-generation H1-antihistamines, second-generation H1-antihistamines have anti-inflammatory effects by inhibiting the release of cytokines from mast cells and basophils, have a longer half-life, and are less soluble in lipids, meaning they are far less likely to cross the blood-brain barrier.[45] In addition, first-generation antihistamines are not recommended due to their safety profile, which includes anticholinergic and sedative effects, as well as interactions with alcohol and other medications such as analgesics and hypnotics. They also reduce REM sleep, learning ability, and impair performance in activities of daily living such as driving.[1,46] In general, the half-life of first-generation H1-antihistamines in the central nervous system is longer than in peripheral blood, meaning their adverse effects last longer than their antihistaminic effect.[46]

There is evidence supporting the use of most second-generation H1-antihistamines in the treatment of urticaria, although no well-designed studies have directly compared the efficacy and safety of different medications. Research has demonstrated the benefit and safety of bilastine,



* For CIndU, individual decisions are based on trigger exposure (eg, cold urticaria in winter).

Figure 4

Management decisions and treatment adjustments for urticaria

CIndU = chronic induced urticaria, d = days, m = months, PROMs = Patient-Reported Outcome Measures, OMA = omalizumab, 2gAH = second-generation H1-antihistamine, UCT = Urticaria Control Test.

Adapted from Zuberbier et al.[1]

cetirizine, levocetirizine, desloratadine, ebastine, fexofenadine, and rupatadine at doses up to 4 times the standard dose.[1]

For AU, the recommended treatment duration with second-generation H1-antihistamines is 2 to 3 weeks. However, more severe cases may require higher doses of antihistamines than those licensed, along with a course of systemic corticosteroids, such as prednisone or prednisolone, at a dose of 1 mg/kg/day for 7 to 10 days.[1,47] In all types of CU, second-generation H1-antihistamines should be maintained long enough to achieve complete symptom control until the patient enters remission.[1]

The treatment should start with the licensed dose of second-generation H1-antihistamines. If symptom control is inadequate, the dose can be increased up to 2 or 4 times the standard. A period of 2 to 4 weeks is generally enough to observe the benefits of the prescribed dose (Figure 5). There is no evidence that combining different antihistamines provides better urticaria control. It is important to note that using higher doses of the same antihistamine has

been shown to be superior to combining different antihistamines for itching control.[1,48,49]

Approximately 61% of patients with CSU do not respond to the licensed dose of second-generation H1-antihistamines, and of these, 63% do not benefit from higher doses. These patients will require second-line therapy with the anti-IgE monoclonal antibody omalizumab.[1,3,50]

Second-line treatment: omalizumab

Omalizumab is recommended as an add-on therapy for patients with CU who are refractory to fourfold doses of second-generation H1-antihistamines.

Omalizumab is the first biologic therapy licensed for the treatment of adults and adolescents (≥ 12 years) with CSU who are unresponsive to second-generation H1-antihistamines.[1] It is a recombinant humanized monoclonal antibody (IgG1) that binds to the Cε3 domain of free IgE, the site of high-affinity IgE receptor (FcεRI) binding on the surface of mast cells and basophils, thus preventing the release of inflammatory mediators.[50,51]

Although the exact mechanism of action of omalizumab is not fully understood, by binding to circulating IgE molecules, it prevents them from attaching to high-affinity receptors on mast cells and basophils. This inhibits mast cell activation and the release of proinflammatory mediators, as well as the recruitment of eosinophils to affected areas. In patients responsive to omalizumab, these cells return to the periphery, normalizing eosinophil and basophil levels and reversing the eosinopenia and basopenia observed in active disease. Additionally, by binding to circulating IgE, omalizumab reduces IgE receptor expression on the surface of mast cells and basophils, further decreasing cell activity. Consequently, patients with autoallergic CSU (Type I) are likely to respond more quickly to omalizumab (early responders), while patients with autoimmune

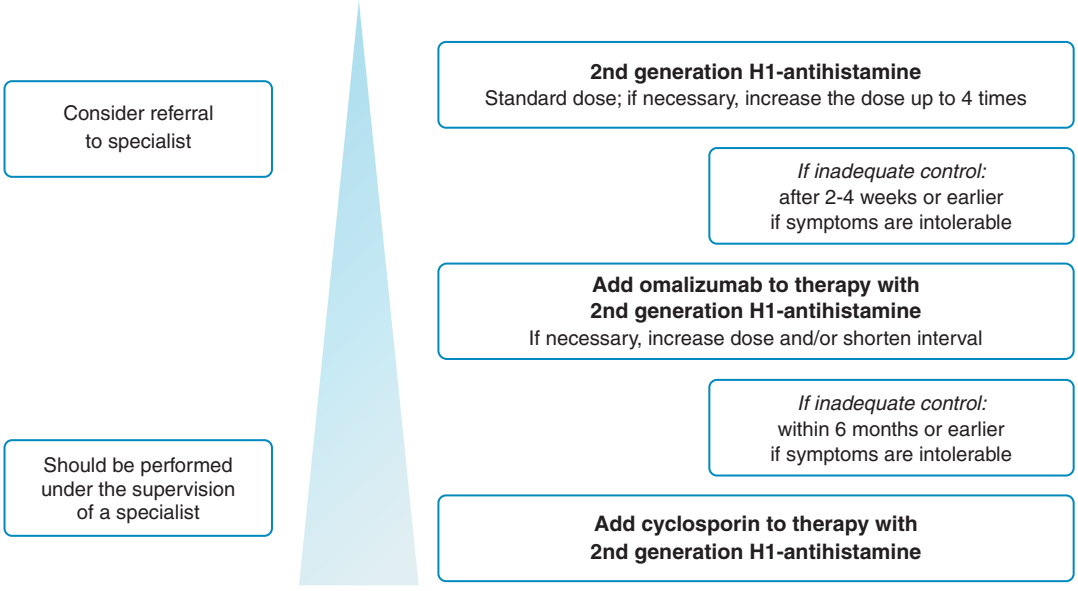


Figure 5
Treatment algorithm for urticaria
Adapted from Zuberbier et al.[1]

CSU (Type IIb) are likely to be late responders, as their response is more dependent on the reduction of high-affinity receptor expression on the membranes of mast cells and basophils. This process is slower for mast cells, taking approximately 70 days to achieve a reduction comparable to that of individuals without the disease.[52]

Omalizumab is available as an injection solution in a single-dose vial (150 mg/vial) or a single-dose prefilled syringe (75 mg and 150 mg). The recommended dose is 300 mg every 4 weeks administered subcutaneously in the deltoid region, lower abdomen, or the thigh. Patients with no history of anaphylaxis may self-administer or have a caregiver administer the medication from the fourth dose onwards, under medical recommendation. Dosing is independent of serum IgE and body weight.[1]

Routine laboratory monitoring is not required before initiating treatment with omalizumab for CSU. However, measuring baseline levels of total serum IgE is recommended, as levels below 40 IU/mL may suggest a suboptimal treatment response.[53,54]

Currently, responders to omalizumab are classified into 2 groups: fast responders, ie, those who achieve symptom control within 4 to 6 weeks; and late responders, ie, those who achieve symptom control only after 12 to 16 weeks.[55] Therefore, nonresponse to omalizumab should not be determine before a minimum of 6 months of treatment.[54] However, approximately 30% of patients remain symptomatic with licensed doses of omalizumab after more than 6 months of treatment.[53]

Optimal management of patients with CSU refractory to omalizumab has not been established. The latest international guidelines suggest gradually increasing the dose to 450 mg/4 weeks and, if necessary, to 600 mg/2 weeks, based on disease activity and control. Higher doses are not recommended due to a lack of clinical evidence. Another option is to reduce the dosing interval to 2 weeks.[50]

There are no biomarkers for urticaria remission, and the total duration of omalizumab treatment for CSU has not been well-defined. After complete symptom control, treatment with omalizumab should be discontinued to assess if the disease is in remission. Thus, after complete CSU control (UCT = 16) for at least 6 months, the decision to discontinue treatment should be individualized.

Strategies for discontinuing omalizumab therapy in CSU include:

1. Immediate discontinuation after complete symptom control, with continuous patient monitoring and retreatment if the disease recurs.
2. Gradually extending the dosing interval weekly until an 8-week interval is reached, followed by discontinuation.

Omalizumab is a safe medication with few side effects, the most common being pain at the injection site, headache, and arthralgia.[56,57] Very rare cases of anaphylaxis have been reported, mostly occurring within the first 3 months of treatment.[58,59] Therefore, the first 3 doses should be administered in a clinic, but home administration is an option from the fourth dose onward.[53]

Omalizumab is not currently licensed for the treatment of CIndU. However, multiple publications, including a systematic review of over 40 studies with several investigator-initiated randomized controlled trials, have demonstrated that most patients with CIndU gain complete or partial control of symptoms with omalizumab.[60] The highest efficacy was observed for cold urticaria, symptomatic dermographism, solar urticaria, heat urticaria, delayed pressure urticaria, and cholinergic urticaria.[60] There is limited evidence for vibratory, aquagenic, and contact urticaria, likely due to their rarity.[60] Unlike CSU, the omalizumab dose for CIndU has not been completely determined, with some studies showing a good response with 150 mg/4 weeks, while others indicate that higher doses may be more effective.[60,61] More controlled clinical trials are needed to clarify this further.

Third-line treatment: cyclosporine A

Cyclosporine A is recommended as an add-on therapy for patients with CU who do not respond to high doses of second-generation H1-antihistamines and omalizumab.

Cyclosporine A (CsA) inhibits the activity of calcineurin, which impairs the production of IL-2, IL-3, IL-4, tumor necrosis factor alpha, and other inflammatory cytokines, thereby inhibiting activated T lymphocytes. Because IL-4 is involved in IgE production, CsA may inhibit IgE-mediated release of histamine and reduce mast cell degranulation.[62]

CsA can be used for the treatment of severe CSU that is refractory to antihistamines and omalizumab (Figure 6). Although its use in urticaria is off-label, there is high-quality evidence supporting this indication, with an overall response rate of 65%.[63]

The recommended dose is 3 to 5 mg/kg/day, and adverse effects are dose- and time-dependent and have been reported in more than 50% of patients treated with moderate doses (4 to 5 mg/kg/day).[47] The main side effects that require monitoring include hypertension, peripheral neuropathy, and increased serum creatinine.[64] CsA should not be used for prolonged periods or in high doses, as there is a risk of malignancies, such as non-melanoma skin cancer, and a higher incidence of infections.[64]

There is no consensus on the best treatment strategy—whether to start with a lower dose and increase it if necessary or to begin with a high dose and reduce it according to the degree of symptom control. However, based on the authors' experience, it is safer to start with lower doses, which can be increased if there is no satisfactory response.

It should be noted that there are no direct comparisons evaluating the efficacy of CsA vs omalizumab. However, a retrospective analysis of patients treated with either CsA or omalizumab showed that CsA is less effective in controlling CSU symptoms.[65] For this reason, and especially due to the potential risk of serious adverse effects, CsA is recommended only in patients who do not respond to omalizumab.[1]

A recent study conducted in Turkey found that patients who responded to CsA were more likely to have elevated CRP, a family history of urticaria, positive autologous serum skin tests, eosinopenia, basopenia, elevated ESR, higher anti-TPO IgG, lower total IgE, and more severe disease activity and poorer disease control—features associated with CSU^{aiTIIb}.[66]

Absolute and/or relative contraindications to CsA include hypersensitivity reactions, concomitant malignancy (except for non-melanoma skin cancer), uncontrolled hypertension, kidney disease, uncontrolled infection, and pregnancy/lactation.[64]

Before starting treatment, patients should be assessed for clinical and laboratory parameters that help identify potential contraindications. Similarly, these parameters are useful in monitoring for potential side effects related to CsA use, such as hypertension and kidney or liver dysfunction.[65,67]

Patients eligible for CsA should have their blood pressure measured on two separate occasions and undergo laboratory tests, including serum urea and creatinine levels, differential blood count, magnesium, lipids, potassium, uric acid, and liver function tests. During treatment, these tests should be performed monthly, as well as whenever the dose is adjusted.[67]

Systemic corticosteroids for the treatment of urticaria

Long-term use of systemic corticosteroids is not recommended in the treatment of urticaria.

Shor-term use of systemic corticosteroid may be considered for the management of exacerbation of chronic urticaria.

Topical corticosteroids should not be used in urticaria.

Corticosteroids (COs) have widespread effects in many organ systems. In the immune system, they may act as anti-inflammatory or immunosuppressants, depending on the dose. The most well-known mechanism involves CO binding to its intracellular receptor, which modulates transcription by either repressing or activating several genes. This classic mechanism occurs a few hours after administration of systemic COs. Recent studies reported that COs have induced faster responses in clinical practice. However, this non-genomic and faster mechanism is not yet fully understood but is suspected to involve receptor interaction with other signaling pathways or even CO binding to other membrane receptors.[68,69]

The first-line treatment for urticaria in emergency care is second-generation H1-antihistamines. In more severe cases, with widespread wheals and/or angioedema, they may be combined with systemic COs. Although this combination is commonly used, robust evidence of its efficacy is limited, as some studies have not shown systemic COs to be effective in AU.[70,71] Upon discharge from emergency care, second-generation H1-antihistamines should be prescribed as the treatment of choice, in doses ranging from 1 to 4 times per day as needed. Oral COs may be added for 7 to 10 days at a dose of 0.5 to 1 mg/kg/day (20 to 60 mg of prednisone or prednisolone in adults). The combination of oral COs with low doses of second-generation H1 antihistamines is not recommended but may be considered in patients who do not respond to fourfold increases in the standard antihistamine dose. In addition, repeated courses of COs should be avoided.[9,70]

In CU, systemic COs may be used for short periods to manage exacerbations. Long-term use of COs should be avoided due to the significant risks outweighing potential benefits. Prolonged use

of corticosteroids is associated with severe side effects, including hypothalamic-pituitary-adrenal axis suppression, osteoporosis with an increased risk of fractures, metabolic and cardiovascular disorders such as diabetes, eye diseases, and a higher risk of infections.[1,72]

Other treatments for urticaria

Currently, no additional therapies are recommended for CSU. However, if a patient does not respond to the therapeutic options suggested by the treatment algorithm described above, alternative options may be considered. These include immunosuppressants such as methotrexate (MTX), azathioprine, mycophenolate mofetil (MMF), and hydroxychloroquine. These treatments are off-label for use in CSU, and studies on these medications are small, uncontrolled, and provide low-quality evidence for their use.[73] In randomized clinical trials, MTX did not show efficacy as an add-on therapy to antihistamines. Azathioprine was effective in refractory cases, while MMF, in less robust studies, showed improvement in symptoms as well as reduction in itching and wheals in patients resistant to antihistamines and corticosteroids. Similarly, hydroxychloroquine was shown to reduce symptoms and improve quality of life.[73,74]

Dapsone is a sulfone antibiotic that has shown some effectiveness in CSU treatment. Studies demonstrated a positive response after 3 months of treatment with dapsone and cetirizine. The effects of dapsone have been reported to last up to 1 year, with significant reduction in itching and severity of symptoms. Other therapies, such as autologous serum therapy and intravenous immunoglobulin (IVIG), have shown mixed results. However, randomized clinical trials are necessary to validate the efficacy of IVIG in reducing urticaria activity.[74]

The identification of different molecular pathways in the pathophysiology of CSU has allowed for the development of more targeted therapies. Biologics have emerged as a promising class in this setting. One example is omalizumab, a drug with anti-IgE properties, which has proven efficacy and widespread use in CSU. Other biologics, such as dupilumab and barzolvolimab, along with new medications such as Bruton tyrosine kinase inhibitors (fenebrutinib and remibrutinib), have emerged as potential treatments and are currently under investigation in randomized clinical trials. Soon, there will be more therapeutic options for patients with refractory CSU.[74]

Treatment of special populations

Children

The treatment of CU in children follows the same algorithm recommended for adults, with second-generation H1-antihistamines being the medication of choice, dosed according to body weight and age. If symptom control is insufficient after 2 to 4 weeks of treatment, it is recommended to increase the licensed dose up to a fourfold.[1]

Although increasing the dose requires caution, the effectiveness of this approach has been demonstrated in pediatric populations, with rates of symptom control ranging from 35% to 92%.[75-77] There are only a few randomized placebo-controlled studies that have tested the safety of increasing the standard dose of second-generation H1-antihistamines up to a fourfold in children, but most have shown similar safety profiles across different dose groups.[78-80]

The choice of which second-generation H1-antihistamine to use in children should take into consideration the child's age and weight, as well as drug formulation, as not all medications are available in solution, drops, or syrup forms. The lowest licensed age for use also varies, starting at 6 months. Second-generation H1-antihistamines recommended and available in Brazil for the pediatric population include bilastine, cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine (Table 7). It should be noted that patients using increased doses of loratadine should have their liver function monitored regularly.[1] First-generation H1-antihistamines are not recommended for use in children, as they cross the blood-brain barrier, leading to disruption of REM sleep and impaired school learning, as well as potentially causing paradoxical excitability, weight gain, and constipation.[1,62] Long-term CO use is not recommended due to side effects, and short courses should only be used as a very restricted measure and dosed according to weight.[1]

In cases refractory to antihistamines, anti-IgE therapy (omalizumab) 300 mg every 4 weeks is recommended and licensed for children with CSU aged 12 or older, as well as for adults.[1] Although there is a lack of controlled studies on the efficacy and safety of omalizumab in children with CU under 12 years old, studies and case series involving this age group have shown good treatment response, with little to no reported adverse events. These studies have shown complete symptom control in 46% to 81% of cases, partial control in 10% to 46%, and a mean treatment

response time of 4 weeks to 3 months. Dosing ranged from 75 mg to 450 mg per month.[82-86] Even though this is an off-label recommendation, omalizumab may be used in refractory CSU in children over 6 years old at doses of 150 mg to 300 mg. Increasing the dose or shortening dosing intervals should be considered for partial responders.

For cases refractory to antihistamines and omalizumab, CsA is indicated. Some studies with children have shown CsA to be both effective and safe and to help reduce chronic CO use. The recommended dose varies from 3 to 4 mg/kg/day given twice daily and can be gradually reduced once urticaria remains controlled for 1 to 3 months. In pediatric studies, complete symptom resolution occurred between 2 days and 3 months from the start of treatment, with little to no adverse events.[87,88]

Most side effects of CsA are related to increased doses and long-term treatment, including hypertension, elevated creatinine, gastrointestinal symptoms, headaches, hirsutism, infections, and paresthesia. Therefore, patients should be assessed for adverse events at least every 4 weeks and the CsA dose should be adjusted once urticaria is controlled to avoid prolonged use.[89]

As in adults, not all children will achieve good symptom control with the recommended treatment options in the algorithm. Staubach et al. reported the cases of 2 children with inadequate response to CsA who were successfully treated with off-label dupilumab 300 mg. The authors suggest that in children with high levels of IgE with inadequate response to omalizumab and CsA, dupilumab may be an option, with doses adjusted according to weight at 200 mg or 300 mg every 2 weeks.[90]

There is insufficient evidence to recommend the use of other immunosuppressants in children with CU. For example, the efficacy of MTX in CSU is uncertain and its use in children has not been investigated.[91] Considering the autoimmune mechanisms of urticaria, there is also no clear evidence that treating autoimmune thyroid diseases impacts the natural course of CU in children. However, hormone replacement therapy is indicated in clinical practice and may have positive effects on CU.[92]

Although there is limited data on the use of high doses of second-generation H1-antihistamines, omalizumab, and CsA in children with CU, current evidence indicates that treatment following the algorithm is effective and safe in this population when administered with caution, respecting age-appropriate doses and monitoring for adverse events.

Pregnant and lactating women

CU mostly affects women of reproductive age, and pregnancy may exacerbate disease activity.[93,94]

During pregnancy, CU tends to improve in half of the patients and worsen in one-third. Some may experience exacerbations, especially in the first and third trimesters, indicating a predominance of Th1 response and proinflammatory signals that activate mast cells. Relevant risk factors for worsening urticaria during pregnancy include mild disease before pregnancy and not being on treatment during pregnancy. Half of the patients whose CU improved during pregnancy reported worsening after giving birth, while half of the patients with worsening CU during pregnancy reported no difference after giving birth.[93]

The international guideline for urticaria recommends the same standard treatment for pregnant and lactating women with CU: start with the licensed dose of second-generation H1-antihistamines, increase the dose up to a fourfold if there is no response, and add omalizumab for refractory patients.[1]

There have been no reports of congenital defects in pregnant women using second-generation H1-antihistamines. Loratadine or cetirizine should be preferred, with possible extrapolation to desloratadine, bilastine, and levocetirizine. These medications are excreted in breast milk in low concentrations. First-generation H1-antihistamines should be avoided during both pregnancy and breastfeeding.[1] It is important to discuss the risks and benefits of treatment with patients, as there is no safety data for increasing the dose of second-generation H1-antihistamines in pregnant and lactating women, but untreated urticaria can be dangerous, with exacerbations of CU being an independent risk factor for preterm birth.[95,96]

Omalizumab is a safe and effective option for pregnant women, women planning to become pregnant, and lactating women with CSU. There is no evidence that the use of this medication increases the risk of adverse events in pregnant women or their infants.[1,94,97,98] Only minimal concentrations of omalizumab are transferred into breast milk, with no reports of complications to the baby during breastfeeding.[99]

Table 7
Standard dosage of second-generation antihistamines for the treatment of urticaria in children[81]

Name	Presentation	Standard dose (as per label)
Cetirizine	Drops (10 mg/mL)	2 to 6 years: 5 drops every 12 hours or 10 drops 1 times/day 6 to 12 years: 10 drops every 12 hours > 12 years: 20 drops 1 times/day
	Oral solution (1 mg/mL)	2 to 6 years: 2.5 mL every 12 hours 6 to 12 years: 5 mL every 12 hours or 10 mL 1 times/day > 12 years: 10 mL 1 times/day
	Tablet (10 mg/tablet)	> 12 years: 1 tablet/day
Levocetirizine	Drops (5 mg/mL)	2 to 6 years: 5 drops every 12 hours > 6 years: 20 drops 1 times/day
	Orodispersible tablet (5 mg/tablet)	> 6 years: 1 tablet/day
Fexofenadine	Oral solution (6 mg/mL)	6 months to 2 years (up to 10.5 kg): 2.5 mL every 12 hours 2 to 11 years (> 10.5 kg): 5 mL every 12 hours
	Tablet (60 mg/tablet) (120 mg/tablet) (180 mg/tablet)	> 12 years: 60 mg/tablet every 12 hours 120 mg/tablet 1 times/day 180 mg/tablet 1 times/day
Desloratadine	Drops (1.25 mg/mL)	6 to 11 months: 16 drops 1 times/day 1 to 5 years: 20 drops 1 times/day 6 to 11 years: 40 drops 1 times/day > 12 years: 80 drops 1 times/day
	Oral solution (0.5 mg/mL)	6 to 11 months: 2 mL 1 times/day 1 to 5 years: 2.5 mL 1 times/day. 6 to 11 years: 5 mL 1 times/day > 12 years: 10 mL 1 times/day
	Tablet (5 mg/tablet)	> 12 years: 1 tablet/day
Loratadine	Oral solution (1 mg/mL)	2 to 12 years: < 30 kg: 5 mL 1 times/day > 30 kg: 10 mL 1 times/day
	Tablet (10 mg/tablet)	> 12 anos: 1 cp 1 vez/dia
Rupatadine	Tablet (10 mg/tablet)	> 12 years: 1 tablet 1 times/day
Bilastine	Oral solution (2.5 mg/mL)	6 to 11 years: 4 mL 1 times/day > 12 years: 8 mL 1 times/day
	Tablet (20 mg/tablet)	> 12 years: 1 tablet 1 times/day

More studies are needed to establish the long-term safety of CSU treatment in this special population.[94]

Older adults

The World Health Organization and the United Nations define "older person," respectively, as those aged between ≥ 60 years and ≥ 65 years. In recent years, people are living longer due to advances in both technology and modern medicine.100 CU is one of the most common pruritic conditions in older adults, with prevalence ranging from 0.2% to 2.8%. Among all patients with CU, 4.1% to 5.5% are in the older age group.[100]

Mean age at diagnosis of CU in this population was 72±5.9 years, and mean referral time to a specialist was 22.8±53 months from the onset of symptoms.[101] CSU was the most common subtype among older people, while symptomatic dermographism was the most common form of CIndU. Furthermore, compared with the adult population, older patients showed a lower rate of atopy, a higher prevalence of age-related comorbidities such as metabolic syndrome, autoimmune disorders, and malignancies, a lower rate of associated angioedema, and lower rates of positive autologous serum skin tests.[100]

Regarding comorbidities, Lapi et al. reported that the risk of developing CU is related to multiple factors. Gastrointestinal diseases were the most common comorbidity, alongside coronary artery disease, cerebrovascular disease, metabolic syndrome, autoimmune diseases, thyroid disorders, psychiatric problems, and malignancies, all reported at high rates in older adults with CU.[100]

Currently, the diagnostic and therapeutic procedures for CU in older patients are the same as those recommended for other age groups.[102] Therefore, treatment of CU in older patients tends to follow the same guidelines for the general population.[100]

The aging process may affect pharmacokinetics and pharmacodynamics, resulting in different treatment responses.[102] Polypharmacy increases the risk of drug interactions that may cause medication safety problems, as well as the risk of low treatment adherence, which in turn can cause suboptimal therapeutic efficacy and lead to poor clinical outcomes.[103] Therefore, the selection of medication and dose for older patients should be considered carefully due to possible drug interactions or adverse effects.[104]

Second-generation H1-antihistamines are recommended as first-line treatment for CU in older patients, with standard doses typically being sufficient to achieve clinical control in most patients.[100] Increasing the standard dose up to a fourfold has also shown good efficacy.[100] However, older patients with multiple comorbidities or kidney/liver dysfunction may require dose adjustments depending on the choice of antihistamine. Bilastine was shown to be safe in these patients.[104]

For patients who do not respond to antihistamine treatment, successful symptom control has been achieved with omalizumab.[100] In refractory cases, other diagnoses related to underlying medical conditions should be considered.[100] However, it should be noted that the differential diagnosis of CU may be more challenging in older adults due to the higher likelihood of other age-specific diseases.[102]

There are no well-defined markers to predict the risk of urticaria recurrence after omalizumab discontinuation in older patients with CSU. However, baseline serum IgG anti-TPO levels and the IgG anti-TPO/total IgE ratio may serve as predictors of CSU recurrence after discontinuation of omalizumab in older patients.[105]

Conclusion

Urticaria is a common and heterogeneous inflammatory skin disease that presents acutely or chronically. Although its chronic form does not have high mortality rates, it significantly affects the quality of life and well-being of patients. Knowledge of the differential diagnoses of urticaria helps reduce the rates of misdiagnosis, leading to adequate management of the condition. The treatment algorithm recommended by international guidelines leads to urticaria control in most patients, but there remains a subset with refractory disease. Several ongoing studies aim to further understand the pathophysiology of urticaria to allow the development of new medications.

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Conflicts of interest: Gabriela Andrade Coelho Dias works as a speaker for Novartis®. Eli Mansour works as a speaker for Novartis®, CSL Behring®, Takeda® e Sanofi®. Regis Albuquerque Campos works as a speaker, advisory board member, and clinical researcher for Novartis®. Solange Oliveira Rodrigues Valle works as a speaker, consultant, and researcher for Novartis®. Luis Felipe Chiaverini Ensina works as a speaker and consultant for Novartis®, Sanofi®, and Abbvie®; and conducts clinical research for Novartis® and Amgen®.

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