

## Consensus on the diagnostic and therapeutic management of chronic spontaneous urticaria in adults – Brazilian Society of Dermatology\*

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**Abstract:** **BACKGROUND:** Urticarias are frequent diseases, with 15% to 20% of the population presenting at least one acute episode in their lifetime. Urticaria are classified in acute ( $\leq 6$  weeks) or chronic ( $> 6$  weeks). They may be induced or spontaneous. **OBJECTIVES:** To verify the diagnostic and therapeutic recommendations in chronic spontaneous urticaria (CSU), according to the experience of Brazilian experts, regarding the available guidelines (international and US).

**METHODS:** A questionnaire was sent to Brazilian experts, with questions concerning diagnostic and therapeutic recommendations for CSU in adults.

**RESULTS:** Sixteen Brazilian experts answered the questionnaire related to diagnosis and therapy of CSU in adults and data were analyzed. Final text was written, considering the available guidelines (International and US), adapted to the medical practices in Brazil. Diagnostic work up in CSU is rarely necessary. Biopsy of skin lesion and histopathology may be indicated to rule out other diseases, such as, urticarial vasculitis. Other laboratory tests, such as complete blood count, CRP, ESR and thyroid screening. Treatment of CSU includes second-generation anti-histamines (sgAH) at licensed doses, sgAH two, three to fourfold doses (non-licensed) and omalizumab. Other drugs, such as, cyclosporine, immunomodulatory drugs and immunosuppressants may be indicated (non-licensed and with limited scientific evidence).

**CONCLUSIONS:** Most of the Brazilian experts in this study partially agreed with the diagnostic and therapeutic recommendations of the International and US guidelines. They agreed with the use of sgAH at licensed doses. Increase in the dose to fourfold of sgAH may be suggested with restrictions, due to its non-licensed dose. Sedating anti-histamines, as suggested by the US guideline, are indicated by some of the Brazilian experts, due to its availability. Adaptations are mandatory in the treatment of CSU, due to scarce or lack of other therapeutic resources in the public health system in Brazil, such as omalizumab or cyclosporine.

**Keywords:** Cyclosporine; Dapsone; Histamine antagonists; Methotrexate; Omalizumab; Urticaria; Urticaria/etiology; Urticaria/therapy

## INTRODUCTION

Urticaria is characterized by the rapid onset of hives (edema in superficial dermis), which may be accompanied by angioedema (edema of deep dermis, fat tissue and gastrointestinal tract).<sup>1,2</sup> Hive, the dermatological lesion, consists of three typical features: (i) central edema of varying size, surrounded by reflex erythema; (ii) associated pruritus; and (iii) transient nature, with the skin returning to its normal appearance usually in a period ranging from 1 to 24 hours.<sup>1,2</sup> Angioedema is defined by: (i) sudden and marked edema of the deep dermis and fat tissue; (ii) greater frequency of pain other than pruritus; (iii) frequent involvement of mucous membranes; and (iv) resolution of the condition at approximately 72 hours, slower than with hives.<sup>1,3</sup>

Urticaria is classified by progression as acute (up to 6 weeks) or chronic (beyond 6 weeks of clinical course).<sup>4,5</sup>

- 1. Guidelines of the International Urticaria Consensus** (EAACI/GA<sup>2</sup>LEN/EDF/WAO (European Academy of Allergology and Clinical Immunology/The Global Allergy and Asthma European Network/The European Dermatology Forum/World Allergy Organization), with participation of the Brazilian Society of Dermatology.

The Guideline of the International Urticaria Consensus of the EAACI/GA<sup>2</sup>LEN/EDF/WAO (European Academy of Allergology and Clinical Immunology/The Global Allergy and Asthma European Network/The European Dermatology Forum/World Allergy Organization), published in 2018, was the result of a systematic with participation of experts, from several medical societies.<sup>5</sup> The quality of the scientific evidence was assessed per the GRA-

DE (Grading of Recommendations Assessment, Development, and Evaluation) method using the GRADE<sup>pro</sup> Guideline Development Tool (GDT).<sup>5</sup>

## CLASSIFICATION<sup>5</sup>

Chronic urticaria (CU) is subdivided into two types: "chronic spontaneous urticaria" (CSU, which is represented by urticaria with hives and/or angioedema of spontaneous onset, with an evolution of over 6 weeks, due to a known cause, such as autoreactivity, resulting from mast cells that are activated by autoantibodies, or unknown causes) and "induced urticarias" (symptomatic dermatographism, cold urticaria, delayed pressure urticaria, solar urticaria, heat urticaria, vibratory angioedema, cholinergic urticaria, and aquagenic urticaria).

In this classification, conditions or diseases that may manifest with urticaria or angioedema, such as urticarial vasculitis, urticaria pigmentosa, autoinflammatory syndromes (in general, periodic syndromes cryopyrin-associated or Schnitzler syndrome), exercise-induced anaphylaxis, Gleich syndrome (episodic angioedema with eosinophilia), Wells syndrome (eosinophilic cellulitis), bullous pemphigoid prior to bullous lesions, angioedema mediated by non-mast cell mediators (in general, bradykinin-mediated angioedema), and other similar diseases, are not considered urticaria subtypes due to their different pathophysiological mechanisms.<sup>5</sup>

## DIAGNOSTIC APPROACH TO CHRONIC URTICARIA<sup>5</sup>

The diagnostic approach was recommended to meet three main objectives: (i) to exclude differential diagnoses, (ii) to assess di-

sease activity and its impact and control, and (iii) to identify triggering or exacerbating agents or, where indicated, any underlying cause. The initial evaluation of patients with CSU should assess the disease activity with tools to which the patient responds (UAS, AAS) and questionnaires on quality of life (CU-Q2oL, AE-QoL) and disease control (UCT), which are indispensable to evaluate impact of the disease, to guide therapy, to help standardization of patient data in the follow-up. It should be emphasized that CSU has an impact in quality of life and a financial impact due to its prolonged treatment.<sup>5-13</sup>

A medical history is essential in patients with urticaria, because of variable triggering and exacerbating factors.<sup>5</sup> Not all factors that are described as causative agents in CU should be investigated in all patients. The first step in the diagnosis is a detailed clinical history that takes into account the following questions:<sup>5</sup>

1. Time of disease onset
2. Shape, size, frequency, duration, and distribution of hives/angioedema
3. Association with angioedema
4. Associated symptoms, such as bone or joint pain, fever, and abdominal pain
5. Personal and family history of hives and angioedema
6. Induction by physical agents or exercise
7. Occurrence in relation to time of day, weekend, menstrual cycle, holidays, and trips to countries abroad
8. Occurrence in relation to foods or medications (non-hormonal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors)
9. Occurrence in relation to infections or emotional stress
10. Prior or concurrent allergies, infections, internal or autoimmune diseases, gastrointestinal problems, or other disorders
11. Social and occupational history, leisure activities
12. Previous treatments and response to treatments, including doses and duration of use
13. Previous diagnostic procedures and their results.

The second step in the diagnosis is to perform a detailed physical examination of the patient.<sup>5</sup> Considering data from the history and physical examination, additional laboratory work up may be requested.<sup>5</sup> Full blood count, ESR (erythrocyte sedimentation rate), and C-reactive protein (CRP) levels are routinely measured.<sup>5</sup> An extended research panel, based on the anamnesis for identifying the underlying causes or inducing factors and for excluding differential diagnoses, may be indicated if there are relevant data from the medical history or physical examination and should include the following measures: 1. suspected triggers (e.g., medications); 2. screening for infectious agents (e.g., *Helicobacter pylori*); 3. thyroid diseases (thyroid hormones and autoantibodies); 4. allergy (intradermal tests and tests to exclude allergens, in general, restriction diet); 5. presence of associated induced-urticaria; 6. associated systemic disease (e.g., serum tryptase levels); and 7. others (e.g., histopathology of skin lesion).<sup>5</sup>

The frequency and relevance of infections vary considerably between patient groups and different areas.<sup>5</sup> Exclusion of malignancies with examinations is indicated only if the patient's history impli-

cates this possibility (in general, sudden and relevant weight loss).<sup>5</sup>

Plasma D-dimer levels are significantly higher in patients with active CSU and decrease according to the clinical response to treatment with omalizumab.<sup>5</sup> The recommendation on measuring D-dimer levels in all patients with CSU is still debated.

#### EVALUATION OF IMPACT OF CSU ACTIVITY AND ITS CONTROL<sup>5</sup>

CSU activity may be evaluated using a simple unified validated system, the UAS7 score.<sup>4,5</sup> UAS7 is based on the evaluation of key properties of urticaria, its signs (hives), and its symptoms (pruritus), which are documented by the patient.<sup>5</sup> UAS7 consists of self-assessment over a 24-hour period once a day for several days, with summing the daily scores over 7 days. Maximum score each for daily hives and symptom intensity is 3, yielding a daily total score of between 0 and 6 and a weekly score of between 0 and 42 (Chart 1 and Figure 1). UAS7 should be performed in the week prior to medical consultation. It is a valuable tool for clinical evaluation of CSU.

The urticaria control test (UCT), in addition to UAS7, has become important in assessing the impact of the disease on quality

**CHART 1: Evaluation of chronic spontaneous urticaria by the Urticaria Activity Score (UAS)**

SCORE*	HIVES	PRURITUS
0	No hives	No symptom
1	Mild (< 20 hives/24 hours)	Mild
2	Moderate (21-50 hives/24 hours)	Moderate
3	Severe (>50 hives/24 hours or large confluent areas of hives)	Intense

\*Sum of scores (hives + pruritus) = (0-6).

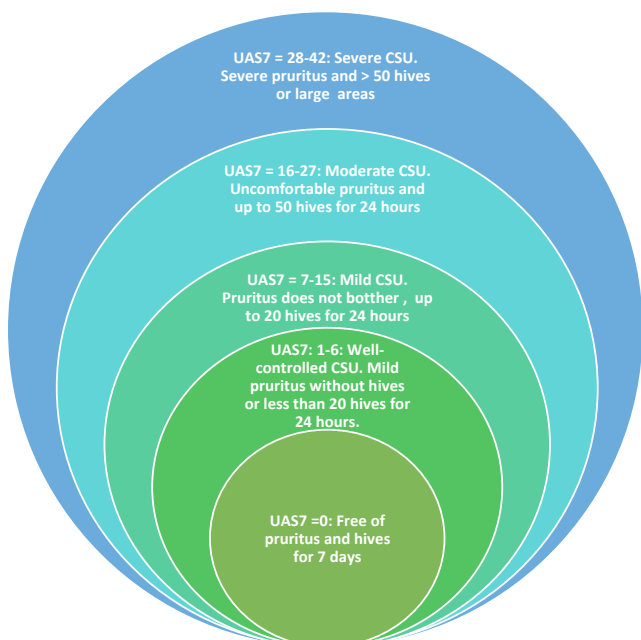


FIGURE 1: Urticaria activity score for seven consecutive days (UAS7)

of life and disease control, both in clinical practice and in research protocols.<sup>5</sup> UCT was developed and validated to determine the level of disease control for all forms of urticaria (CSU and induced urticaria), because UAS does not evaluate angioedema or induced urticarias.<sup>5</sup> UCT is composed of only four items, defining the limit between “well-controlled disease” and “poorly controlled disease;” thus, it is usable in clinical practice, with a cutoff point for “well-controlled disease” ranging from 12 and 16.<sup>5</sup> The score varies from 0 to 16 and higher values reflect better disease control. It is an instrument that helps guide therapeutic decisions.<sup>5</sup>

UCT is under validation in Brazil by the Department of Allergy and Immunology of UFRJ, and the Portuguese version is described in chart 2.

**MANAGEMENT OF PATIENTS WITH URTICARIA**<sup>5</sup>

Three basic considerations are proposed in the treatment of these patients:

- a) The goal is to treat urticaria until it enters remission
- b) The therapeutic approach involves several aspects, such as:
  - Identification and elimination of underlying causes when possible

- Eliminate triggering factors
- Induction of tolerance in induced urticaria when possible
- Use of pharmacological agents in the prevention of degranulation and the release of mast cell mediators and their effects
- The treatment should follow the basic principles of treating as much as necessary and as little as possible; e.g., advancing in steps or retroactively in stages in the therapeutic escalation according to the course of disease.

In order to eliminate an underlying cause, an accurate diagnosis is necessary.<sup>5</sup> The identification of a cause for CU, however, is difficult in most cases; for example, with infections, which may be a cause or an aggravating factor or have no relation to CU.<sup>5</sup> The only definitive proof of the causal nature of a suspected or triggering agent is the remission of symptoms following its removal and their recurrence following re-exposure in a double-blind challenge.<sup>5</sup> In practice, this approach is often not feasible. Spontaneous remission of urticaria may occur over time. Urticaria may go into remission with the elimination of a suspected cause or triggering factor coincidentally, without any cause-effect relationship.<sup>5</sup>

Pharmacological treatment of CSU has, as main goal, to relieve symptoms by reducing the effects of mast cell mediators, such as histamine and platelet-activating factor (PAF) and others, on target organs and tissues.<sup>5</sup> Many symptoms of urticaria are mediated primarily by the actions of histamine on H1 receptors on endothelial cells (resulting in hives) and sensory nerves (neurogenic erythema and pruritus).<sup>5</sup> Thus, continuous treatment with antihistamines is fundamental in the treatment of urticaria; safety data are available for continuous use over several years.<sup>5</sup>

Other mast cell mediators (PAF, leukotrienes, and cytokines) may be involved, and a pronounced cellular infiltrate, including basophils, lymphocytes, and eosinophils, can be seen in the lesions.<sup>5</sup> These patients may respond completely to a brief course of corticosteroids and be relatively refractory to antihistamines.<sup>5</sup>

First-generation antihistamines have prominent anticholinergic effects and sedative actions on the central nervous system (CNS) and have many interactions with alcohol and drugs that affect the CNS, such as analgesics, hypnotics, sedatives, and mood-altering substances.<sup>5</sup> They can interfere with rapid eye movement sleep (REM sleep) and impact learning and cognitive performance.<sup>5</sup> Interference with the CNS is observed especially in multiple concurrent tasks and the performance of complex sensorimotor tasks, such as driving vehicles,<sup>5</sup> and should be indicated with caution. First-generation antihistamines with more pronounced adverse effects are promethazine, diphenhydramine, ketotifen, and chlorpheniramine.<sup>5</sup>

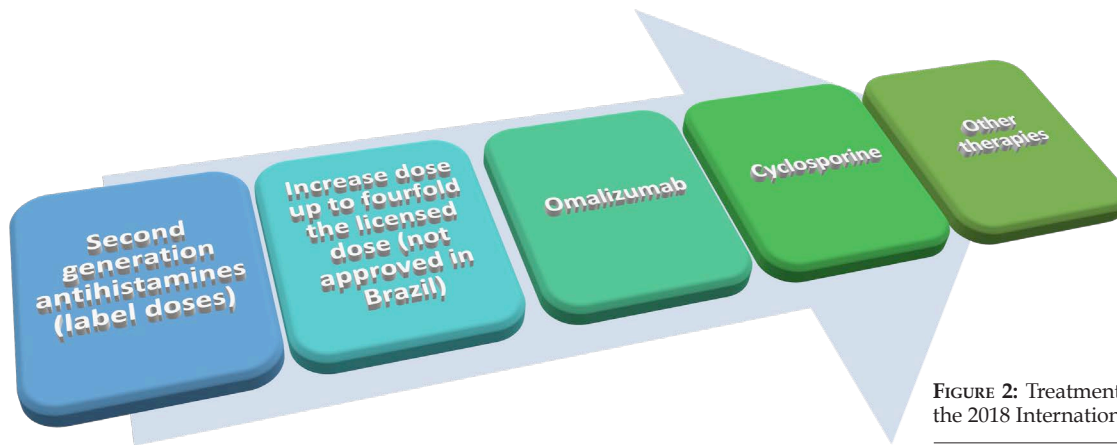
The recommended treatment algorithm for CU, per the 2018 International Guideline, is summarized in figure 2.<sup>5</sup>

**INTERNATIONAL GUIDELINE 2018 - TREATMENT**

**First-line pharmacological treatment:**

Oral antihistamines are key drugs in the treatment of chronic urticaria, especially nonsedating and low-sedating agents: H1 receptor antagonists, such as cetirizine, fexofenadine, loratadine, and ebastine and, more recently, levocetirizine, desloratadine, rupa-

CHART 2: Urticaria Control Test (UCT)	
1. How much have you suffered from the physical symptoms of urticaria (itching, hives, or swelling) in the last 4 weeks?	<input type="radio"/> very much <input type="radio"/> much <input type="radio"/> somewhat <input type="radio"/> a little <input type="radio"/> not at all
2. How much has your quality of life been adversely affected by urticaria in the last 4 weeks?	<input type="radio"/> very much <input type="radio"/> much <input type="radio"/> somewhat <input type="radio"/> a little <input type="radio"/> not at all
3. How often was the treatment for your urticaria insufficient to control symptoms in the last 4 weeks?	<input type="radio"/> very much <input type="radio"/> much <input type="radio"/> somewhat <input type="radio"/> a little <input type="radio"/> not at all
4. Overall, how well have you had your urticaria under control in the last 4 weeks?	<input type="radio"/> very much <input type="radio"/> much <input type="radio"/> somewhat <input type="radio"/> a little <input type="radio"/> not at all
Interpretation of UCT	The questionnaire has 5 possible answers for each question: very much (a score of 0), much (1), somewhat (2), a little (3), and not at all (4). The total UCT score in this short version of the four questions ranges from a minimum of 0 (totally uncontrolled disease), to a maximum of 16 (best possible control of urticaria).



**FIGURE 2:** Treatment scheme proposed by the 2018 International Urticaria Guideline

Adapted from: Zuberbier, et al, 2018.<sup>5</sup>

tadine, epinastine and bilastine.<sup>5</sup> Their efficacies are similar; however, due to the absence of hepatic metabolism, fexofenadine, desloratadine, and bilastine are indicated in liver diseases.<sup>5</sup>

#### Second-line pharmacological treatment:

A retrospective study with 549 CSU patients showed that more than 75% of subjects were refractory to first-line treatment with second-generation anti-H1 drugs, with only 31.8% of patients attaining complete control of disease with the use of the licensed doses. UAS7 was the only predictor of refractoriness to treatment with anti-H1.<sup>14</sup>

According to the Urticaria International Guideline, as second-line of treatment, use of up to fourfold doses of second-generation antihistamines is indicated, whenever licensed dose failed to control the disease.<sup>4,5</sup> The use of these drugs at maximum doses, such as desloratadine 20 mg/day, levocetirizine 20 mg/day, loratadine 40 mg/day, and cetirizine 40 mg/day, is not yet approved in Brazil, despite published international scientific literature.<sup>15</sup> Due to their safety profile, in CSU patients without arrhythmia, without nephropathy or hepatopathy, these drugs may be indicated, with minimal side effects and increased efficacy, when doses are increased.<sup>5,16,17</sup> Liver enzymes monitoring is indicated during this type of therapeutic approach, with careful patient orientation.<sup>3</sup>

Although antihistamines achieve CSU control when used at up to 4-fold the licensed doses, in many patients with CSU, alternative treatments may be required. Before changing the treatment to alternative therapies (adjuvants), it is recommended to wait 1-4 weeks to achieve complete effectiveness of the drugs that are in use.<sup>5</sup>

Because the severity of urticaria may vary and because spontaneous remission may occur over time, therapeutic re-evaluation of the need for continued treatment or a separate or adjunctive treatment is also recommended every 3 to 6 months.<sup>5</sup>

#### Third-line pharmacological treatment:

In recent years, the use of biological agents for urticaria, particularly omalizumab, has become more prominent as a third-line agent in chronic urticaria that is refractory to initial approaches (first- and second-lines of treatment).<sup>18</sup> Omalizumab is a humanized

monoclonal antibody against the  $\epsilon$ 3 domain of IgE, which lies near the binding site for Fc $\epsilon$ RI receptors on mast cells and basophils and Fc $\epsilon$ R2.<sup>5</sup> The doses of omalizumab that have been used in several studies for chronic refractory urticaria have ranged from 150-300mg subcutaneously, once a month; ideal dose for urticaria is 300mg every 4 weeks.<sup>3</sup> On average, half of all patients (52%) controlled their urticaria (UAS7  $\leq$  6) after the 12<sup>th</sup> week versus 62% after the 24<sup>th</sup> week in phase III studies of the molecule; 11% did not respond to treatment.<sup>19</sup> Initial treatment should be continued for 24 weeks.<sup>19</sup> The total treatment duration for chronic urticaria has not been established; thus, the decision to discontinue treatment should be individualized.

The proposed mechanism of action for this drug is based on the finding that when there are high circulating IgE levels in the blood, mast cells and basophils express higher amounts of Fc $\epsilon$ RI receptors on their membranes, becoming vulnerable to binding with anti-Fc $\epsilon$ RI $\alpha$  IgG autoantibodies. Doses of omalizumab in CSU independent of serum IgE levels. The approved doses, and the treatment duration may vary by country.<sup>5</sup> In Brazil, omalizumab was approved for CSU in children aged over 12 years, at 300 mg subcutaneously every 4 weeks for 6 consecutive months.

#### Treatment of Exacerbations

Oral corticosteroids, particularly prednisone at doses of 20-50mg per day, may be necessary for short periods of use (7 days, maximum 10 days) for significant exacerbations of chronic urticaria that does not respond completely to antihistamines or for sporadic episodes of exacerbation.<sup>5</sup> Prolonged use should be avoided due to the side effects and development of comorbidities.<sup>5</sup> Their use should be avoided for more than 7 days each month. There is a strong recommendation for only using systemic corticosteroids under specialist supervision in the treatment of CSU.<sup>5</sup>

#### Fourth-line pharmacological treatments

Despite the absence of strong published scientific evidence, all fourth-line drugs may be valuable for patients in certain cases of refractoriness in the earlier stages, in the appropriate clinical settings.<sup>5</sup>

In patients with severe disease and persistent progression, with treatment failure to previous measures, cyclosporine therapy



is an option to refractory CSU. Cyclosporine acts by inhibiting IL-2 production in lymphocytes. In urticaria, it is believed that an additional mechanism of action is its reduction of immunoglobulin production and reduction of the high-affinity IgE receptor. It has been studied in cohorts and placebo-controlled studies at doses of 1 to 5mg/kg/day. The effective dose in chronic urticaria appears to be 3 mg/kg/day for periods of 8 to 16 weeks, yielding success rates of 64% to 95%.<sup>20,21</sup> It is important to emphasize that before use, patients should perform blood pressure measures and evaluate renal function, magnesium, uric acid, and potassium; these tests should be repeated periodically.<sup>20</sup> Side effects appear to be dose-dependent and occur in more than half of all patients who are treated with moderate doses (4 to 5mg/kg/day).<sup>21</sup>

#### Other Treatments

Other non-licensed medications should be used in patients in whom previous steps of treatment failed. They have a low level of recommendation and have only been presented in case reports and studies of small series.<sup>5</sup>

a) Anti-inflammatory drugs: dapson, colchicine, and montelukast are medications that present clinical studies with low scientific evidence.<sup>5,22-24</sup> Montelukast showed good response in 20% to 50% of patients who did not responded to therapy with antihistamines alone.<sup>25</sup> Reeves *et al.*<sup>26</sup> studied 18 CU patients who had been treated with hydroxychloroquine for 12 weeks, noting disease control and improved quality of life. This drug is relatively safe, but the possibility of retinopathy should be monitored.

#### b) Other Immunosuppressants

- Methotrexate has been used at a mean weekly dose of 15 mg.<sup>27</sup> This drug has anti-inflammatory and immunomodulatory properties, and its mechanism of action comprises an increase in adenosines, apoptosis of CD4 lymphocytes, and inhibition of neutrophil chemotaxis.<sup>27,28</sup>

- Other oral drugs, with immunomodulatory and immunosuppressive effects, such as sulfasalazine, mycophenolate mofetil, azathioprine, cyclophosphamide, and tacrolimus. are available for use in CSU.<sup>5</sup> There are no controlled studies, with relevant number of patients and efficacy; they may be used as alternatives on failure with conventional therapy.<sup>5</sup>

#### c) Other Immunobiologicals:

- Anti-tumor necrosis factor (TNF) medications are indicated in CU due to increased production of TNF, implicated in the pathogenesis of the disease. Etanercept, infliximab, and adalimumab have been used in case reports and small series for various types of urticaria.<sup>29</sup>

- Interleukin 1 antagonists (anti-IL-1: canakinumab, anakinra), although formally indicated for autoimmune diseases, have been used in urticaria due to inflammatory cytokine production in the disease.<sup>29</sup> Canakinumab is under investigation in a placebo-controlled study, but the results have not been made available.<sup>29</sup>

- Rituximab (anti-CD20) is a chimeric monoclonal antibody against CD20, expressed on B cells, that decreases autoantibody production. The recommended dose is 375mg/m<sup>2</sup>. There are few case reports using this drug.<sup>29</sup>

- Intravenous immunoglobulin (IVIg) is an IgG purified

polyclonal preparation derived from the plasma of several donors. In urticaria, IVIg has an immunomodulatory effect decreasing IgG anti-FcεRII and IgG anti-IgE.<sup>29</sup> Studies with series of patients showed improved response at a dose of 0.4mg/kg/day for 5 days. It may lead to rare side effects, such as kidney failure and anaphylactic reactions.<sup>29</sup>

#### US GUIDELINE 2014- TREATMENT<sup>30</sup>

##### First-line treatment

The US Guideline for CSU, published in 2014, indicates use of second-generation anti-histamines (sgAH) at licensed doses as first-line of treatment.

##### Second-line of treatment

As second-line of treatment up-dosing (up to 4-fold) of second-generation antihistamines is indicated; furthermore, add other sgAH, H2-antagonists, anti-leukotriene (montelukast) or first-generation antihistamines at bedtime.

##### Third-line treatment

If there is no control with the previous steps, hydroxyzine or doxepin are indicated, as third-line treatment.

##### Fourth-line treatment

As fourth-line of treatment, omalizumab or cyclosporine are indicated, as well as, other anti-inflammatory drugs, immunosuppressants or immunobiological drugs (dapson, sulfasalazine, hydroxychloroquine, colchicine, tacrolimus, mycophenolate mofetil, sirolimus, cyclophosphamide, methotrexate, IVIg, anti-TNF, anti-IL-1 receptor and anti-CD20).<sup>31</sup>

Figure 3 shows the differences between the Internacional and US Guidelines in CSU.<sup>32</sup>

##### Pregnancy and lactation

Regarding treatment during gestation, to date, there are no reports of congenital defects in women who have used second-generation anti-H1 antihistamines during pregnancy.<sup>5</sup> However, few studies are available regarding the use of cetirizine,<sup>33</sup> and a large meta-analysis has examined the use of loratadine.<sup>34</sup> Loratadine is metabolized in the liver, whereas desloratadine is not.<sup>5</sup> Due to safety profile, the preferred second-generation anti-histamines in pregnancy are loratadine, (with possible extrapolation to desloratadine) and cetirizine (with possible extrapolation to levocetirizine).<sup>5</sup> All anti-H1 antihistamines are excreted in human milk at low concentrations.<sup>5</sup> First-generation anti-H1s should be avoided during breastfeeding.<sup>5</sup> Omalizumab use in pregnancy has shown no evidence of maternal or fetal harm.<sup>5,35-37</sup>

##### Data obtained from the questionnaire sent to Brazilian experts

Sixteen specialists answered the questions that were sent about the number of patients who were seen in clinical practice, diagnostic procedures, and the treatment of CSU (Chart 3). Data concerning the questionnaire are summarized in table 1. The number of CSU patients who were seen by the participants varied: 7 par-

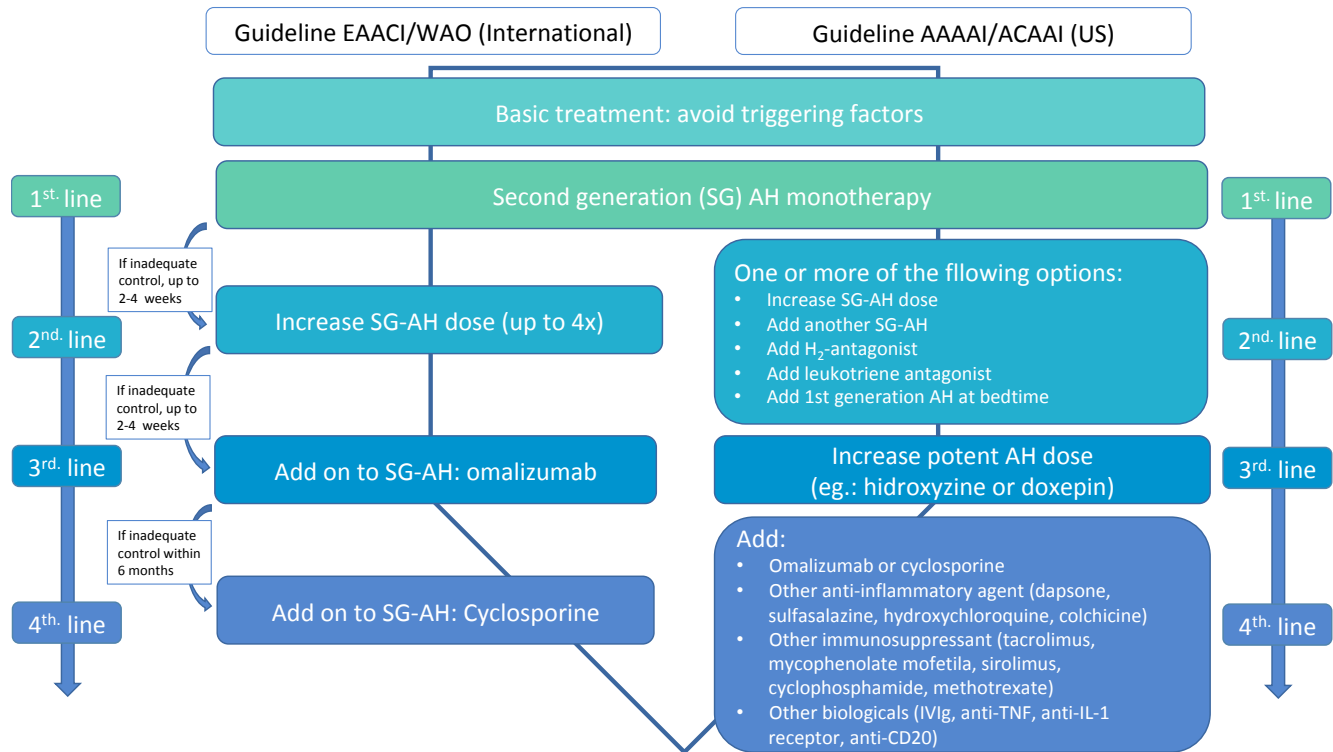


FIGURE 3: Differences between the Internacional and US Guidelines in CSU

Adapted from: Zuberbier, et al, 2018.<sup>32</sup>

ticipants (44%) attended up to 10 patients/month, 1 (6%) between 11-20 patients/month, 7 (44%) between 21-50 patients/month, and 1 (6%) between 51-100 patients/month, most of whom were part of public services. Participants reported that they conducted their CSU patients based on published treatment protocols in the international literature-63% in the International Guideline,<sup>5</sup> and 13% in the US Guideline-but 50% of participants made use of recommendations from various treatment protocols or a combination of them.

Laboratory tests were requested as required in the examination of CSU by 81% of participants; 19% did not request any tests. The most frequently requested tests (>50%) were full blood count, ESR, CRP, free T4, and TSH. The least commonly requested tests (50%) were autoantibodies to thyroid, stool parasitology, plasma D-dimer levels, hepatitis serology (particularly hepatitis B and C), ANA, total complement and fractions, total serum IgE, liver enzymes (AST, ALT, ALP, and gamma GT), renal analysis (urea and creatinine), and chest X-ray. Skin biopsy of the urticarial lesion and histopathology were indicated by 94% of participants in treatment-refractory patients or on suspicion of urticarial vasculitis, of whom 38% also performed direct immunofluorescence.

In the public service, within the treatment options for CSU, 81% of participants used non-sedating antihistamines (second-generation) as the initial option, versus 19% who administered sedating antihistamines (first-generation). As the second therapeutic option, 81% offered non-sedating antihistamines at doses of 1 to 4-folds the licensed dose; 13% used sedating antihistamines, and 6% indicated

methotrexate, in addition to antihistamine treatment. As subsequent options, the use of cyclosporine, methotrexate, dapson, montelukast, cyclosporine, systemic corticosteroids (short-term), and omalizumab were reported.

In private care, of the therapeutic options that are offered to patients with CSU, 94% used non-sedating antihistamines as the first option versus 6% for sedating antihistamines. As the second option, 81% administered non-sedating antihistamines at doses of 1 to 4-folds the licensed dose, compared with 13% for sedating antihistamines and 6% for omalizumab. Subsequent options included cyclosporine, dapson, systemic corticosteroid (short-term), methotrexate and montelukast.

Regarding the side effects of medications, 56% of participants questioned the safety of continuous prescription of sedating antihistamines (first-generation). Further, 81% of participants opined that the prescription of non-sedating antihistamines at doses higher than those licensed was safe.

Regarding the indications for omalizumab use, when the antihistamines that were used did not show significant efficacy, 69% of participants favored its use, despite its high cost.

For other treatment options, after non-sedating antihistamines and omalizumab, participants indicated dapson, colchicine, methotrexate, H2 antihistamines, cyclosporine, and montelukast.

Regarding lifestyle habits for CSU patients, 81% of participants suggested that patients should avoid use of nonhormonal anti-inflammatory drugs; 50% advised that foods with dyes and

**CHART 3: Questionnaire on chronic spontaneous urticaria (CSU): Diagnosis and treatment - Brazilian Society of Dermatology**

- 1. Inform number of patients with CSU attended per month (estimate)**  
 1-10  11-20  20-50  50-100  >100
- 2. Performed care:**  
 public service %  private clinic %
- 3. Do you follow the treatment protocol already established?**  
 yes  no
- 4. Which protocol?**  
 own  consensus. Which? (International, US)
- 5. What is your CSU treatment management in the public service? State your options used in your public practice?**
- 6. What is your CSU treatment management in the private clinic? State your options used in your private practice?**
- 7. Do you perform routine exams in your investigation of CSU?**  
 yes, specify  no
- 8. Do you have a habit of recommending avoiding the use of nonhormonal anti-inflammatory drugs to all patients with CSU?**  
 yes, specify  no
- 9. Do you have a habit of recommending avoiding the frequent use of food with colorings and preservatives and alcoholic beverages to all patients with CSU?**  
 yes, specify  no
- 10. Do you have a habit of inquiring about the aggravation or seasonality of urticaria in relation to the perimenstrual period for all female patients with CSU?**  
 yes, specify  no
- 11. Do you have a habit of inquiring about the presence of recurrent fever, arthralgia/arthritis, enlarged lymph nodes, or residual spots on the skin of patients with CSU when taking their medical history?**  
 yes, specify  no
- 12. Do you question patients with CSU about the presence at home or professional contact with dogs or cats, based on the possibility of toxocaríasis?**  
 yes, specify  no
- 13. Are you comfortable prescribing first-generation antihistamines continuously to patients with CSU?**  
 yes, specify  no
- 14. Are you comfortable with prescribe second-generation antihistamines in duplicate, triplicate, or even quadruplicate doses to all patients with CSU, even if these doses are not recommended in the package inserts (off-label)?**  
 yes, specify (if you increase the number of tablets every few days or you already start quadruplicate doses on failure of the package insert dose after it has been ineffective for at least 15 days after its prescription)  no, specify
- 15. In patients who do not get their CSU under control (pruritus, hives or angioedema, UAS7, Urticaria Activity Score 7 days <6) with the use of quadruplicate doses of second-generation antihistamines, do you agree with maintaining antihistamines use and adding omalizumab for at least 6 months, as indicated in the biological medication package insert?**  
 yes, specify  no, specify
- 16. In patients who do not control their CSU (pruritus, hives or angioedema, UAS7<6) with the use of quadruplicate doses of second-generation antihistamines, with the addition of omalizumab, for at least 6 months, what medications would you use as the third therapeutic option (you can select more than one medication if you have experience with them in CSU and remember that all of them are off-label uses in CSU)?**  
 montelukast  dapsone  colchicine  methotrexate  cyclosporine  sulfasalazine  intravenous immunoglobulin  
 mycophenolate mofetil  anti-TNF- $\alpha$  biological agent  rituximab  anti-H2 antihistamine (cimetidine, ranitidine)
- 17. In patients without a history that is suggestive of CSU-associated diseases and who have a normal physical examination, what ancillary exams do you usually request (you can select more than one alternative if you think it is appropriate for patients with CSU, both as a diagnostic aid and as a result of medications that you will prescribe)?**  
 Full blood count  ESR  CRP  3 stool parasitological examinations  D-dimer levels  liver function  kidney function  
 total IgE levels  thyroid autoantibodies  upper digestive endoscopy with examination for *Helicobacter pylori*, in case of dyspeptic symptoms  RAST (*Immucap*) for food allergens, inhalants, and insects
- 18. In patients with CSU, do you instruct them to complete the UAS7 the week before consultation and the UCT (Urticaria Control Test), referring to the last week before consultation?**  
 yes, specify  no, specify
- 19. Do you find flaws in the understanding and completion of the UAS7 and UCT by patients?**  
 yes  no
- 20. For patients who continue to experience urticarial lesions and symptoms of pruritus or burning, even after 1 month of full antihistamine therapy with quadruplicate doses of second-generation anti-H1 after at least 2 months of continuous use, do you indicate cutaneous biopsy to rule out urticaria vasculitis? Do you perform direct immunofluorescence?**  
 Skin biopsy (histopathology)  yes, specify  no  
 Direct immunofluorescence of skin biopsy (DIF)  yes, specify  no

ESR: erythrocyte sedimentation rate; CRP: c-reactive protein



TABLE 1: Treatment of chronic spontaneous urticaria (CSU): Brazilian Society of Dermatology 2018

			% total de respostas
N patients attended		n<50	94%
SCU/ month		n≥50	6%
Follow treatment based on published guidelines?		International	63%
		United States	13%
		Others/combination*	50%*
Most requested laboratory tests		Blood count, ESR, CRP, free T4, TSH	≥50%
		Stool Parasitologic Examination, thyroid autoantibodies, D-dimer, hepatitis serologies, ANA, complement, IgE, hepatic enzymes	<50%
Indicates histopathological examination if urticaria vasculitis is suspected?		Yes	94%
		No	6%
Treatment (public service)	1 <sup>st</sup> option	non-sedating AH (2nd generation)	81%
		sedative AH (1st generation)	19%
	2 <sup>nd</sup> option	non-sedative AH (2nd generation) with dose increased 1-4x	81%
		sedative AH	13%
		Methotrexate	6%
Treatment (private practice)	1 <sup>st</sup> option	non-sedating AH (2nd generation)	94%
		sedative AH (1st generation)	6%
	2 <sup>nd</sup> option	non-sedative AH (2nd generation) with dose increase 1-4x	81%
		sedative AH	13%
		Omalizumab	6%

n: number; SCU: spontaneous chronic urticaria; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TSH: thyroid stimulating hormone; ANA: antinuclear antibody; IgE: immunoglobulin E; AH: antihistamines; \*8/16 of specialists use a combination of treatment protocols.

preservatives should be avoided; 75% questioned patients about perimenstrual aggravation (autoimmune progesterone dermatitis in the differential diagnosis); 13% inquired about the possibility of infestation by *Toxocara canis* (toxocariasis) due to the presence of domestic animals; and 94% considered the association with other general symptoms, such as fever and arthralgia.

For the evaluation of CSU activity, 62% of participants indicated the use of the UAS-7 form but noted inadequate comprehension and completion by many patients with CSU.

















## CONCLUSIONS

CSU treatment is constant evolving and remains a permanent challenge in most patients. This position paper, from sixteen Brazilian experts, based on data from literature and the International and US Guidelines, made the following recommendations to tailor it to actual clinical practice in Brazil in the public and private service:

1. There is no need for extensive work up in CSU if medical history and physical examination do not address the need for further laboratory testing other than general laboratory evaluation.
2. Antihistamine treatment should be continuous and always aim for complete disease control (UAS7=0) or UCT>12.
3. The use of medications at non-licensed doses, especially second-generation antihistamines, is supported by the literature; however, patients should understand and accept to use them. Monitoring cardiological and hepatic parameters (in antihistamines with liver metabolism) are always indicated.
4. Omalizumab is a safe and approved drug for use in CSU that is refractory, as adjuvant therapy to antihistamines anti-H1; its indications should be under the guidance of a team of experts in urticaria.
5. Other adjuvant drugs are available for *off-label* use in Brazil; thus, they may be useful and necessary for refractory cases of CSU, with strict clinical and laboratory monitoring and information of the possible benefits and risks when using them. □

## REFERENCES

1. Zuberbier T, Greaves MW, Juhl L, Kobza-Black A, Maurer D, Stingl G, et al. Definition, classification, and routine diagnosis of urticaria: a consensus report. *J Invest Dermatol Symp Proc*. 2001;6:123-7.
2. Cooper KD. Urticaria and angioedema: diagnosis and evaluation. *J Am Acad Dermatol*. 1991;25:166-74.
3. Criado PR, Criado RF, Maruta CW, Reis VM. Chronic urticaria in adults: state-of-the-art in the new millennium. *An Bras Dermatol*. 2015;90:74-89.
4. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69:868-87.
5. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. 2018;73:1393-414.
6. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. *Br J Dermatol*. 1997;136:197-201.
7. Parisi CA, Ritchie C, Petriz N, Morelo Torres C. Direct Medical Costs of Chronic Urticaria in a Private Health Organization of Buenos Aires, Argentina. *Value Health Reg Issues*. 2016;11:57-9.
8. DeLong LK, Culler SD, Saini SS, Beck LA, Chen SC. Annual direct and indirect health care costs of chronic idiopathic urticaria: a cost analysis of 50 nonimmunosuppressed patients. *Arch Dermatol*. 2008;144:35-9.
9. Williams PV, Kavati A, Pilon D, Xiao Y, Zhdanava M, Balp MM, et al. Treatment Patterns, Healthcare Resource Utilization, and Spending Among Medicaid-Enrolled Children with Chronic Idiopathic/Spontaneous Urticaria in the United States. *Dermatol Ther (Heidelb)*. 2018;8:69-83.
10. Broder MS, Raimundo K, Antonova E, Chang E. Resource use and costs in an insured population of patients with chronic idiopathic/spontaneous urticaria. *Am J Clin Dermatol*. 2015;16:313-21.
11. O'Donnell BF. Urticaria: impact on quality of life and economic cost. *Immunol Allergy Clin North Am*. 2014;34:89-104.
12. Al-Ahmad M, Alowayesh MS, Carroll NV. Economic burden of refractory chronic spontaneous urticaria on Kuwait's health system. *Clinicoecon Outcomes Res*. 2016;8:163-9.
13. Graham J, McBride D, Stull D, Halliday A, Alexopoulos ST, Balp MM, et al. Cost Utility of Omalizumab Compared with Standard of Care for the Treatment of Chronic Spontaneous Urticaria. *Pharmacoeconomics*. 2016;34:815-27.
14. Curto-Barredo L, Archilla LR, Vives GR, Pujol RM, Giménez-Arnau AM. Clinical Features of Chronic Spontaneous Urticaria that Predict Disease Prognosis and Refractoriness to Standard Treatment. *Acta Derm Venereol*. 2018;98:641-7.
15. Weller K, Ziege C, Staubach P, Brockow K, Siebenhaar F, Krause K, et al. H1-antihistamine up-dosing in chronic spontaneous urticaria: patients' perspective of effectiveness and side effects--a retrospective survey study. *PLoS One*. 2011;6:e23931.
16. Zuberbier T. Pharmacological rationale for the treatment of chronic urticaria with second-generation non-sedating antihistamines at higher-than-standard doses. *J Eur Acad Dermatol Venereol*. 2012 ;26:9-18.
17. Ortonne JP. Urticaria and its subtypes: the role of second-generation antihistamines. *Eur J Intern Med*. 2012;23:26-30.
18. Asero R, Tedeschi A, Cugno M. Treatment of refractory chronic urticaria: current and future therapeutic options. *Am J Clin Dermatol*. 2013;14:481-8.
19. Zhao ZT, Ji CM, Yu WJ, Meng L, Hawro T, Wei JF, et al. Omalizumab for the treatment of chronic spontaneous urticaria: A meta-analysis of randomized clinical trials. *J Allergy Clin Immunol*. 2016;137:1742-50.e4.
20. Koski R, Kennedy KK. Treatment with omalizumab or cyclosporine for resistant chronic spontaneous urticaria. *Ann Allergy Asthma Immunol*. 2017;119:397-401.
21. Kulthanan K, Chaweekulrat P, Komoltri C, et al. Cyclosporine for Chronic Spontaneous Urticaria: A Meta-Analysis and Systematic Review. *J Allergy Clin Immunol Pract*. 2018;6:586-99.
22. Criado RF, Criado PR, Martins JE, Valente NY, Michalany NS, Vasconcellos C. Urticaria unresponsive to antihistaminic treatment: an open study of therapeutic options based on histopathologic features. *J Dermatolog Treat*. 2008;19:92-6.
23. Morgan M, Cooke A, Rogers L, Adams-Huet B, Khan DA. Double-blind placebo-controlled trial of dapsone in antihistamine refractory chronic idiopathic urticaria. *J Allergy Clin Immunol Pract*. 2014;2:601-6.
24. Pho LN, Eliason MJ, Regruto M, Hull CM, Powell DL. Treatment of chronic urticaria with colchicine. *J Drugs Dermatol*. 2011;10:1423-8.
25. Tedeschi A, Airaghi L, Lorini M, Asero R. Chronic urticaria: a role for newer immunomodulatory drugs? *Am J Clin Dermatol*. 2003;4:297-305.
26. Reeves GE, Boyle MJ, Bonfield J, Dobson P, Loewenthal M. Impact of hydroxychloroquine therapy on chronic urticaria: chronic autoimmune urticaria study and evaluation. *Intern Med J*. 2004;34:182-6.
27. Sagi L, Solomon M, Baum S, Lyakhovitsky A, Trau H, Barzilai A. Evidence for methotrexate as a useful treatment for steroid-dependent chronic urticaria. *Acta Derm Venereol*. 2011;91:303-6.
28. Perez A, Woods A, Grattan CE. Methotrexate: a useful steroid-sparing agent in recalcitrant chronic urticaria. *Br J Dermatol*. 2010;162:191-4.
29. Ferrer M, Madamba R. Biologics in chronic urticaria. *Allergol Immunopathol (Madr)*. 2017;45 (Suppl 1):S41-4.
30. Bernstein JA, Lang DM, Khan DA, Craig T, Dreyfus D, Hsieh F, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;133:1270-7.
31. Antia C, Baquerizo K, Korman A, Alikhan A, Bernstein JA. Urticaria: A comprehensive review: Treatment of chronic urticaria, special populations, and disease outcomes. *J Am Acad Dermatol*. 2018;79:617-33.
32. Zuberbier T, Bernstein JA. A Comparison of the United States and International Perspective on Chronic Urticaria Guidelines. *J Allergy Clin Immunol Pract*. 2018;6:1144-51.
33. Weber-Schoendorfer C, Schaefer C. The safety of cetirizine during pregnancy. A prospective observational cohort study. *Reprod Toxicol*. 2008;26:19-23.
34. Schwarz EB, Moretti ME, Nayak S, Koren G. Risk of hypospadias in offspring of women using loratadine during pregnancy: a systematic review and meta-analysis. *Drug Saf*. 2008;31:775-88.
35. Namazy J, Cabana MD, Scheuerle AE, Thorp JM Jr, Chen H, Carrigan G, et al. The Xolair Pregnancy Registry (EXPECT): the safety of omalizumab use during pregnancy. *J Allergy Clin Immunol*. 2015;135:407-12.
36. Ghazanfar MN, Thomsen SF. Successful and Safe Treatment of Chronic Spontaneous Urticaria with Omalizumab in a Woman during Two Consecutive Pregnancies. *Case Rep Med*. 2015;2015:368053.
37. Wood RA, Khan DA, Lang DM, Fasano MB, Peden DB, Busse PJ, et al. AAAAI Response to the EAACI/GA(2)LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria 2017 Revision. *Allergy*. 2018 [Epub ahead of print].

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