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Acute and Chronic Urticaria Diagnosis and Management Taking into Account Their Differences

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Abstract

Purpose of review Urticaria is a frequent disorder that can present with erythema, edema, and pruritus involving the skin and mucous membranes. Early diagnosis and proper management of the urticaria according to the type (i.e., acute vs chronic) is of utmost importance to reduce the burden of the disease and prevent psychosocial comorbidities. In this review, we aim to summarize the diagnosis and management of acute and chronic urticaria with emphasis on the differences.

Recent findings Autoimmune mechanisms (type I or type IIb autoimmunity) have been recently defined in the pathogenesis of chronic spontaneous urticaria. Despite the high rates of symptom control in both acute and chronic urticaria with the existing treatment options, new treatments are still needed in a subset of patients. Promising treatment targets in CSU include Bruton's tyrosine kinase, Siglec-8, or IL-4/13.

Summary Therapeutic management of acute and chronic urticaria is still challenging despite the highly effective treatments. In addition to symptomatic treatment, elicitation of the pathogenesis of both forms of urticaria and clear understanding of the nature of the disease by the patient are essential. Urticaria has still a high impact on the patients' quality of life warranting the studies on the pathogenesis, novel treatment options, and the factors determining which patients with acute urticaria will likely develop chronic urticaria.

Introduction

Urticariais a skin disease with systemic pathogenic involvement that is expressed in the skin and in the mucous membranes in a very special way with erythema, edema, and pruritus and with the basic peculiarity that the lesions are evanescent, fleeting. Its clinical expression is very varied and very often it is experienced by the patient with anguish because he does not know why it happens and trying to find a reason, he often cannot find it. Early diagnosis by the general practitioner and typing of the type by the specialist physician is important. With the aim of showing the specific approach to acute urticarias with respect to chronic ones, this review has been developed and we hope it is useful.

Definition

Urticaria with or without angioedema is characterized by pruritic evanescent erythematous and edematous papules or plaques [1].

The most recent European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization (EAACI/GA^{2}LEN/EDF/WAO) guidelines classify urticaria into acute and chronic urticaria [1].

Urticaria is defined traditionally as acute (AU) if symptoms evolve for ≤ 6 weeks and chronic (CU) if evolve for > 6 weeks. To guarantee a stable CU, 3 to 6 months of evolution tend to be required in clinical research. CU can be divided into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CINDU) [1].

Pathogenesis

Both acute and chronic urticaria are a mast cell–driven disease characterized by hives and angioedema. Mast cell activation induces degranulation of vasoactive substances such as histamine, platelet activating factor, prostaglandins, and leukotrienes as well as other proinflammatory mediators including cytokines (IL-1, IL-4, IL-13, IL-5, IL-17, IL-24, or TNF-alfa among others) and chemokines. As a result, vasodilatation and an increase in the vascular permeability occur, facilitating plasma extravasation and recruitment of inflammatory cells (T-cells) [2, 3]. Pruritus is induced by stimulation of sensory skin nerves [4, 5].

Different types of receptors have been identified in mast cell membranes which explains why mast cell activation is driven by different triggers which differ between AU and CU. Some examples include cytokine receptors (IL-4R, IL-5R, IL-3R), chemokine receptors (CCR), toll-like receptors (TLR9, TLR7), complement receptors (C5aR, CD88, CD35), prostaglandin receptors (CRTH2), MRGPRX2, Siglec-8, and immunoglobulin (Ig) receptors (FcεRI, FcγRIIb) [2].

Type I hypersensitivity (HS) or IgE-mediated urticaria has been involved in both AU and CU pathogenesis. In AU, environmental antigen-IgE complexes

bind Fc receptors on the mast cell membrane inducing its activation. Foods and drugs are the most common responsible allergens in AU. Nevertheless, in most of the cases, AU is a consequence of mast cell activation through other receptors and not necessarily type I hypersensitivity is involved. This is the case of AU induced by non-steroidal inflammatory dugs, infections, or emotional factors. In CU, IgE antibodies (autoallergy) against thyroperoxidase (TPO), thyroglobulin, tissue factor, or IL-24 have been identified provoking mast cell degranulation [6–8]. In contrast, type IIb autoimmune urticaria or IgG-mediated urticaria has only been described in a subset of patients with CU where mast cell can be activated by the complex IgE-IgG, IgG, and less frequently IgM, and binds to the alfa-subunit of the high-affinity IgE receptor (FcεRI) [9, 10]. CU can suffer exacerbations independently of FcεRI through alternative mechanisms. Finally, it is known that circulating immune complexes (CIC) can interact with receptors for the Fc portion of Igs (FcR) of mast cells. This fact could explain flares during lupus erythematosus or infections where CIC are produced [11].

Neurotransmitters, neurohormones, neuropeptides, and complement molecules (C5a anaphylatoxin) have also a role in the pathogenesis of both AU and CU, involved among others in mast cell and chemoattracted inflammatory cells activation [12].

Epidemiology, and burden of the disease

Urticaria can occur at any age and affects 1% of the global population. Due to its prevalence, it has a tremendous personal, social, and economic impact [13].

AU is estimated to have an overall lifetime prevalence of 12–23.5%. AU is more prevalent in individuals with atopic diseases although we all could suffer it once along the life [14, 15]. Its sudden appearance involving large body areas with a common face involvement showing hives or angioedema impacts directly in the patient agenda and is a common consultation in the emergency areas.

CU is estimated to have an overall lifetime prevalence of 0.7%. CU prevalence varies from 0.23 to 1.8% depending on the geographic area. CU is two times more frequent in women than in men. CU is more prevalent among individuals between 40 and 60 years. Recent data shows an increase in the prevalence of CU [13]. CU is associated with many comorbidities including autoimmunity, infective diseases, atopic/allergic diseases, and metabolic syndrome [15, 16••, 17–20]. Its long-lasting course being in 60% of the patients of 3 to 5 years and the fact that almost 20% of the patients can suffer more than one CU episode along their life requires a correct approach to each patient according to each phenotype. It has been estimated a delay of its diagnosis of 2–4 years in Western Canada or Latin America [21, 22].

Clinical manifestations, including angioedema

Both AU and CU are clinically characterized by the appearance of evanescent wheals (< 24 h). Wheals consist of pruritic pale to pink-red edematous papules or plaques. Lesions can have central clearing with a peripheral erythematous rim. Acute urticaria in children can be manifested as annular or polycyclic lesions, resolving with a dusky hue (urticaria multiforme), which can be confused with erythema multiforme [1]. All the body surfaces can be involved in one patient and in any episode of AU and CU suggesting that all the skin is reactive to the triggers and is prone to develop the lesions. Because the highest number of mast cells are located at the hands, feet, and face, clinical expression in these sites shows many times angioedema.

Some patients with AU and CU will present angioedema in addition (up to one-third in CU patients), or even just angioedema. Angioedema consists of swelling of the deep dermis, subcutaneous tissue, and mucous membranes (mouth, respiratory and gastrointestinal tract). Angioedema lesions can be painful apart from pruritic. Lesions can last up to 72 h [1].

Both AU and CU can be associated with systemic symptoms. AU may present with dyspnea, nausea, diarrhea, abdominal pain, or headache, especially when angioedema is present. In some cases, anaphylaxis can occur specially when the AU cause is due to a true type I hypersensitivity. Severe CU can be associated with fatigue, sweats and chills, indigestion or arthralgias, and certain forms of inducible CU as, e.g., cold, cholinergic, or contact urticaria [23].

Types of acute and chronic urticaria

AU can be classified into 2 categories:

- **Non-allergic AU (NAAU):** it is the result of mast cell activation by foods, drugs, and infections by non-allergic mechanisms [17–19, 24, 25].
- **Allergic AU (AAU):** a history of < 2 h exposure to drugs, foods, or insect venoms prior to development of wheals and/or angioedema should raise the possibility of allergic AU. In contrast to NAAU, systemic symptoms like respiratory or digestive symptoms are more frequent. In severe cases, anaphylactic shock can occur. AAU occurring > 2 h of allergen exposure include exercise-induced food anaphylaxis, alpha-galactosidase anaphylaxis, anisakis simplex anaphylaxis, and AU of immunological contact [1].

CU can be classified into 2 groups:

- **Chronic spontaneous urticaria (CSU):** there is not an identified trigger inducing wheals and/or angioedema [1]. An autoimmune mechanism has been proposed for CSU. According to that, 2 types of autoimmune CSU have been described [2] (Table 1).
- **Chronic inducible urticaria (CINDU):** wheals and/or angioedema appear after exposure to a certain trigger [26] (Table 2).

Table 1. Types of autoimmune urticaria

	Type I autoimmunity or autoallergy	Type IIb autoimmunity
Mechanism	IgE against different autoantigens (TPO, TG, IL-24)	IgG against IgE and FcεRI
Prognosis	Moderate severity and activity Short duration	High severity and activity Long duration
Other autoimmune comorbidities	Lower	Higher
Total IgE	Normal or high	Low
Basopenia and eosinopenia	Less	More
Diagnosis	Total auto-IgE and specific IgE to autoantigens	ASST + BHRA/BAT + WB/ELISA for IgG
Treatment response	Higher response to H1-antihistamines Higher and faster response to omalizumab	Lower response to H1-antihistamines Lower and slower response to omalizumab

(*ASST*, autologous serum skin test; *BHRA*, basophil histamine release assay; *BAT*, basophil activation test; *ELISA*, enzyme-linked immunoabsorbent assay, *IgE*, immunoglobulin E; *TPO*, thyroperoxisade; *TG*, thyroglobulin; *WB*, western blot)

Table 2. Types of CINDU

CINDU type	Trigger	Diagnostic tools
Symptomatic dermographism	Rubbing, scratching, scrubbing	Moderate scratching of the skin with: - Blunt smooth object - Fric test (4 pins) - Dermographic tester (36 g/mm^2)
Cholinergic urticaria	Sweating	Exercise machines
Cold urticaria	Cold solids, liquids, or air	Ice cube test, assess critical stimulation time threshold (CsTT) TempTest, assess critical temperature threshold (CTT)
Delayed pressure urticaria	Vertical pressure	Suspension of weights over shoulder
Heat urticaria	Hot solids, liquids, or air	Heat source TempTest
Solar urticaria	UVA, UVB, visible light	UVA radiation UVB radiation Projector (visible light)
Aquagenic urticaria	Water, sweat, saliva, tears, ambiental humidity	Soaked compressed or towel
Vibratory angioedema	Vibration (including laughing, applauses, machines)	Vortex vibrator
Contact urticaria	Latex, animal products, vegetables/fruits, chemicals	Skin prick test Closed patch tests Open controlled application testing

Table 3. Trigger factors in AU and CU

AU	CU
- Infections (viral: COVID-19, herpes, viral hepatitis; bacterial: *Helicobacter pylori*, *Streptococcus*, *Staphylococcus*, *Mycoplasma pneumonia*, *Salmonella*, *Brucella*, *Mycobacterium leprae*, *Borrelia*, *Chlamydia pneumonia*, *Yersinia enterocolítica*; parasitic: *Anisakis simplex*, fungal) - Medical drugs (NSAID, antibiotics, radiocontrast media) - Foods (children > adults) - Insect bites - Contact allergy - Blood transfusions - Vaccinations	- Infections (viral: COVID-19, herpes, viral hepatitis; bacterial: *Helicobacter pylori*, *Streptococcus*, *Staphylococcus*, *Mycoplasma pneumonia*, *Salmonella*, *Brucella*, *Mycobacterium leprae*, *Borrelia*, *Chlamydia pneumonia*, *Yersinia enterocolítica*; parasitic: *Anisakis simplex*, fungal) - Medical drugs (ACE, NSAID) - Foods (CU < AU) - Emotional stress

(*ACE*, angiotensin-converting enzyme inhibitors; *NSAID*, nonsteroidal anti-inflammatory drugs)

Table 4. Complementary tests for CSU diagnosis

Test	Utility
ASST	Injection of autologous serum collected during disease activity from some patients with chronic spontaneous urticaria (CU) into clinically normal skin elicits an immediate weal and flare response. This observation provides a convincing demonstration of a circulating factor or factors that may be relevant to the understanding of the pathogenesis and management of the disease. It should be regarded as a test for autoreactivity rather than a specific test for autoimmune urticaria Tend to be positive in CSU with type IIb autoimmunity
BHRA/BAT	In vitro test for detecting basophil histamine release activity or basophil activation (CD63–CD203) induced by patient's serum on a healthy donor Positive in CSU with type IIb autoimmunity
IgE and IgG anti-TPO and anti-Tg	Ig-E positive against TPO/IL-24 in CSU with type I autoimmunity Ig-G anti-TPO and anti-TG, most common in type IIb autoimmunity
Baseline IgE against FcεRI	High normal levels predict favorable response to H1-antihistamines and omalizumab and low or very low levels can show slow response or even no response to omalizumab
Skin biopsy	Indicated if other differential diagnoses are proposed
PCR, VSG and D-dimer	Higher levels are associated with higher activity and poorer treatment response
Provocation tests (see Table 2)	Diagnosis of CINDU

Trigger factors

Many trigger factors have been described in AU and CU [17–19, 24, 25] (Table 3).

Urticaria in children vs adults

The urticaria developed in children shows a broad differential diagnosis ranging from benign and self-limited hypersensitivity responses to multisystem inflammatory diseases. Clinically the cutaneous hives and angioedema are associated with more permanent and even purpuric lesions.

Pediatric AU has a prevalence of 13.9%. It constitutes a frequent reason of consulting emergency services. The main cause of AU episodes is infections (respiratory > gastrointestinal > otitis media). It has a good prognosis with an excellent response to H1-antihistamines. Rarely it progresses to CU [27, 28].

On the other hand, CU has a higher prevalence in children compared to adults (1.43% vs 0.86%). In contrast to adults, it is more common in males. The median age of onset is 5–9 years. As in adults, CSU is more common than CINDU (80% vs 20%). The most common type of CINDU in pediatric population is symptomatic dermographism (40%). Fifty percent of CSU cases resolve in 5 years and 45.4% of cases resolve in 6 years [29, 30].

Urticaria diagnostic approach

In a patient with a clinical suspicion of urticaria, the first step is to classify it into AU (< 6 weeks) or CU (> 6 weeks) [1].

In AU, no complementary tests are needed. We will try identifying the trigger in order to eliminate it and we will proceed to treat it with H1-antihistamines. It is important to inform the patient of the possibility of chronification [1].

In CU, three elements are important in the diagnosis procedure. First, is to identify the elementary lesion that characterizes urticaria and urticarial rashes. Urticaria might present with hives (wheals) and/or angioedema, the latter involving the deeper mucocutaneous layers. We need to consider potential differential diagnosis including urticaria vasculitis, cutaneous/systemic mastocytosis, anaphylaxis, and autoinflammatory diseases. Information regarding duration, frequency, diurnal variation, size/shape/color/distribution of lesions, and subjective symptoms must be collected. In case of angioedema, a detailed description of location, extension, time of appearance, triggers, and symptoms must be done. Mucosal edema (gastrointestinal and respiratory) has to be investigated as well. Systemic symptoms as well as involvement of other organs have to be excluded. As in AU, triggers should be ruled out as well as atopic/allergic comorbidities. Second, we must elucidate if there is any physical factor inducing the formation of wheals/angioedema in order to differentiate between CSU and CINDU. And check if different types of urticaria can be suffered simultaneously by the same patient. Third, laboratory tests have a very limited role in the diagnosis. ASST, BHRA/BAT, and WB/ELISA can be performed in order to classify CU according to the autoimmune mechanism. Nevertheless except for the ASST, this laboratory approach is just done by specialized centers and is not available by routine in most of the departments. A blood test including complete blood count, C-reactive protein, thyroid function test, liver and kidney functions, complements (C3, C4, C1q, CH50), and IgE and excluding infections is often performed. Looking for the baseline total IgE and the IgG against TPO has been suggested as useful parameters helping to identify quite well the subgroup of CSU patients with type IIb autoimmunity. Skin biopsy is performed when hives long-last more than 24 h or when CU is especially refractory to standard treatments which is the case of atypical urticaria [31].

Complementary tests useful, which ones and when must be used, for what

AU don't precise complementary tests. Some complementary tests can be used to aid CU diagnosis as well establishing prognosis and treatment response (Table 4).

Patient-reported outcome measures (PROMs)

The fluctuating and unpredictable course of the episodes of urticaria has a substantial impact on the daily life of patients. Factors such as decreased sleep quality and social isolation also contribute to the deterioration in the quality of life (QoL), particularly in chronic urticaria [32, 33]. Probably due to the self-limiting course of acute urticaria, its impact on the quality of life of the patients is somewhat overlooked. An early study showed little impairment of quality of life in patients with acute/intermittent urticaria compared to chronic forms of urticaria [34]. However, in another study, the mean DLQI score was 11.05 in patients with acute urticaria indicating a very large effect on the quality of life [35]. On the other hand, the impact of chronic urticaria on the quality of life was investigated comprehensively, the impact of CSU on QoL was significant in numerous studies, and comparable to psoriasis, atopic dermatitis, and even coronary artery disease [36–38].

The use of PROMs is critical when evaluating and monitoring different aspects of urticaria such as disease activity, disease severity, disease control, and quality of life [39]. The use of patient-reported outcome measures as the primary target of treatment has also been recommended by task forces and guidelines [40, 41••]. PROMs can be specific for urticaria (Urticaria Activity Score (UAS); Urticaria Control Test (UCT); Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL)), angioedema (Angioedema Activity Score (AAS); Angioedema Control Test (AECT); Angioedema Quality of Life Questionnaire (AE-QoL)), or generic for skin diseases (Dermatology Life Quality Index (DLQI)). Although there are various PROMs that are routinely used to assess disease severity, disease activity, and quality of life in chronic urticaria, most of the abovementioned PROMs are not validated for acute urticaria; moreover, there is no specific PROMs available for acute urticaria, only generic PROMs for skin diseases can be used at the moment.

In acute urticaria, a 10-point visual analogue scale (VAS) for pruritus was frequently used to assess the disease severity [42, 43]. Previously, different VAS and Likert-type PROMs were used to evaluate CSU activity, as well. However, these heterogeneous scoring systems made it difficult to compare results between different studies [39]. As a result, the use of validated severity scores such as UAS is recommended in treatment guidelines. UAS7 is the most used tool and often seen as the gold standard for measuring the activity of urticaria disease in routine clinical practice [44]. UAS is a prospectively reported, CSU-specific tool used to assess overall CSU activity, severity, and treatment response. It has two components that evaluate the severity of itching (ranging from 0 to 3) and the number of urticarial lesions (ranging from 0 to 3). The daily UAS score ranges between 0 and 6. When the daily UAS score is summed for 7 consecutive days, the weekly UAS score (UAS7) is calculated (0–42 points). Although there is no generally accepted consensus on the UAS7 cut-off values, a UAS7 score of 0 indicates a remission of symptoms, and a score of 6 or less indicates minimal disease activity. According to the proposed classification, a UAS7 score between 7 and 15 indicates mild disease activity, between 16 and 27 indicates moderate disease activity, and between

28 and 42 indicates severe disease activity [45]. The minimal clinically important difference (MCID) in the UAS7 score is reported as a decrease between 9.5 and 10.5 points [46]. Although the UAS and UAS7 are widely used for the evaluation of patients with CSU, they are not still available for the use in acute urticaria. Validated scoring systems such as UAS are needed in acute urticaria for the better disease monitoring and comparison of different studies.

UAS has also some limitations. First, since it is a prospective measurement questionnaire, it is difficult to evaluate the disease activity in the first visit of the patient. Also, it requires a high level of patient compliance for daily reporting. Moreover, it does not consider the angioedema and CIndU symptoms in scoring.

UCT was developed to overcome these limitations. UCT is a questionnaire that evaluates the last 4 weeks retrospectively, consists of 4 questions, and evaluates disease control. The questions ask about the severity of physical symptoms, the effect of symptoms on quality of life, how often treatment fails to control symptoms, and how well symptoms are controlled in general. Each response is scored between 0 and 4 points, resulting in a total score ranging from 0 to 16 (0: uncontrolled disease, 16: complete control). A UCT score of 11 and below indicates poor disease control, and a score of 12 and above indicates well-controlled disease [47]. The MCID value for UCT was determined as 3 points [48]. The fact that UCT can be evaluated retrospectively enables evaluation of disease control at the first visit. Other advantages are that it can be filled quickly and easily. Unlike UAS, it can be used for all types of chronic urticaria. The current international guidelines recommend the use of UCT score when deciding treatment modifications [41••].

The CU-Q2oL is a CSU-specific, 23-item scale. The questions evaluate different aspects of CSU's impact on patient's lives. These include itching, swelling, daily activities, sleep, appearance, and limitations [49]. Each question is scored between 1 and 5, with a higher score showing a worse quality of life. The MCID was determined as 15 points [50].

The AAS is a five-item questionnaire that evaluates disease severity in recurrent angioedema. In different questions, the duration of the angioedema, the severity of the physical discomfort, the ability to do daily activities, the cosmetic effect, and the global severity assessment are assessed [51]. The score of each question varies between 0 and 3. The daily AAS score ranges from 0 to 15, the weekly AAS score ranges from 0 to 105, and the 28-day AAS score ranges from 0 to 420 [51]. AECT is a retrospectively completed, 4-item scale, similar to UCT. There are two versions of AECT evaluating the last 4 weeks or 3 months. The cut-off value of AECT for a well-controlled disease is 10 points [52]. The AE-QoL is a 17-item scale that evaluates the angioedema-related quality of life. Seventeen questions are related to areas such as the ability to work, fatigue, mood, fears, embarrassment, and food. The total score ranges from 0 to 85, with higher scores indicating the worse quality of life [53].

Skin disease–specific scales include DLQI and Skindex-29. Those allow a comparison of the effects of other skin diseases and urticaria on quality of life [54]. The DLQI is a 10-item questionnaire that is generally used to evaluate the quality of life associated with skin diseases. The questions evaluate the symptoms, social activities, work/school life, personal relationships, and treatment. Each question is scored between 0 and 3, resulting in a total score

ranging from 0 to 30. A higher score indicates the worse affected quality of life [55]. The minimal clinically important difference for DLQI in chronic urticaria patients was 2.24–3.10 [56]. The DLQI was also used to evaluate QoL in patients with acute urticaria in a number of studies [34, 35].

Altogether, the use of PROMs is a crucial part of both clinical practice and research in CSU monitoring and choosing the right treatment. Validated scales are available in many languages for the assessment of the disease-related quality of life, disease activity, and disease control. However, there is still an unmet need as few scales have been developed specifically for the assessment of CIndUs and none for AU. It is also important to keep in mind that the use of MCID values rather than merely statistical significance is required to better interpret the clinical relevance of the changes and to have a significant effect on patient care.

Treatment

International treatment guidelines recommend a stepwise treatment approach in the treatment of urticaria. The first-line pharmacological treatment for both acute and chronic urticaria is modern 2nd-generation H1-antihistamines. In patients who do not respond to standard doses, increasing the antihistamine dose up to 4 times has been found to be effective and safe. In AU, the H1-antihistamines either at standard or high doses can adequately control symptoms in most of the patients. On the other hand, in patients with CSU, symptoms can be controlled in approximately only four out of 10 patients with standard doses of H1-antihistamines, while a well-controlled disease can be provided in 63% of the non-responders with higher dose H1-antihistamines [57].

Because the H1-antihistamines adequately control the symptoms in most of the patients with AU and the AU resolves spontaneously over a few weeks, proper counselling of the patients about the self-limiting course of the disease is usually sufficient in AU. However, despite the conflicting evidence for the use of oral or parenteral corticosteroids in addition to H1-antihistamines in the treatment of AU, corticosteroids are still used quite frequently, particularly in emergency services [58–60]. In a randomized placebo-controlled double-blind study, the use of 40 mg/day oral prednisone treatment for 4 days in addition to 5gm/day oral levocetirizine treatment did not provide any benefit in terms of symptom control and relapse [42]. Another study showed no benefit of adding IV corticosteroids to antihistamine treatment, while oral corticosteroid use was associated with persistent urticaria activity [43]. Despite the lack of well-designed RCTs and high level of evidence, current treatment guidelines recommend the use of short-term oral corticosteroids for a maximum of 10 days in the treatment of AU episodes [41••].

On the other hand, in patients with CU whose symptoms cannot be controlled despite the treatment with standard and high-dose antihistamine treatment, adding omalizumab at a dose of 300 mg/4 weeks to the treatment is the treatment of choice. The patients unresponsive to standard-dose omalizumab therapy can be treated with higher doses of omalizumab up to 600 mg every

2 weeks (either by increasing the four-weekly dose or shortening the dose intervals). A meta-analysis of real-life studies of omalizumab in CSU has reported complete and partial response in 72% and 18% of the patients, respectively [61]. In patients who do not respond to H1-antihistamines and omalizumab, the recommended treatment option is cyclosporine which has been shown to be effective in RCTs [62, 63]. In addition to these treatment options, oral corticosteroids can be used for a period not exceeding 10 days to control acute exacerbations. Doxepin, methotrexate, montelukast, dapsone, sulfasalazine, warfarin, tranexamic acid, narrowband UVB phototherapy, autologous serum, and colchicine are among the treatments that are not included in the treatment algorithm because the level of evidence is not as high as these treatments, but there are studies and case series showing that they are effective in the treatment of chronic urticaria [41••].

Future treatments

Although AU often resolves spontaneously and adequate symptom control can be obtained with H1-antihistamines in majority of the patients, novel treatments leading to a more rapid symptom relief and more effective prevention of relapses are needed. Despite the early reports indicating a role for systemic corticosteroids, recent RCTs failed to show any benefit in AU. Future studies with larger number of patients on the effect of corticosteroids and antihistamine combination on symptom control and AU course are warranted. In line with this, there is only one randomized clinical trial registered on clinicaltrials.gov which compares the efficacy of oral levocetirizine plus oral prednisone to oral levocetirizine alone in AU patients. However, the results of this study have not been posted yet (NCT03545464). The use of omalizumab in patients with AU has not been reported in the literature, although there is a clinical trial which has not been updated since the initial registration (NCT02191072). Considering the safety profile of corticosteroids, omalizumab might be a good second-line treatment alternative in patients with AU for rapid control of the symptoms and prevention of the recurrences. The potential use of omalizumab in AU should be considered for the future.

On the other hand, with the addition of omalizumab to the therapeutic armamentarium, current treatments in chronic urticaria provide effective and safe symptom control in most of the patients. However, despite the high response rates, symptoms cannot be fully controlled with current treatment options in a group of patients. Considering the patients with type IIb autoimmune CSU (positive autologous serum skin test, positive basophil histamine release assay, lower IgE levels) have lower response rates and slow response with omalizumab, novel treatments are still needed [64, 65].

Dupilumab

Dupilumab is a monoclonal antibody directed against the alpha subunit of IL-4 and IL-13 receptors and used in the treatment of atopic dermatitis, nasal

polyposis, and asthma [66]. In a case series of 6 patients, dupilumab treatment was shown to be effective in patients with omalizumab-resistant CSU and atopic dermatitis, in line with previous studies showing increased IL-4 and Th1/Th2 response in CSU patients [67, 68]. In a phase III study, dupilumab treatment resulted in a significant reduction in pruritus and urticaria scores in antihistamine-resistant CSU patients, while the primary endpoints were not met in omalizumab-resistant patients [69, 70]. Phase II and phase III studies investigating the efficacy of dupilumab treatment in CSU, cholinergic urticaria, and cold urticaria are ongoing (NCT05526521, NCT03749148).

Bruton's tyrosine kinase inhibitors (remibrutinib, rilzabrutinib)

Bruton tyrosine kinase is expressed in various hematopoietic cells including macrophages, mast cells, and basophils. In addition to its role in B cell development, it is involved in signal transduction and FcεRI activation in mast cells [71, 72]. Considering the role of FcεRI signaling in CSU, BTK inhibitors may play a role in the treatment of CSU. In a phase II trial comparing fenebrutinib and placebo treatment in 93 CSU patients, the reduction in UAS7 scores at the end of 8 weeks was significantly higher in the treatment arm but its development for CSU was stopped [73]. Another BTK inhibitor, remibrutinib, acts by covalently binding to BTK and its effect is thought to be faster and longer lasting. A more significant improvement in UAS7 scores and quality of life was achieved with remibrutinib in a placebo-controlled study [74, 75]. Phase III studies on the efficacy and safety of remibrutinib therapy in CSU are ongoing (NCT05048342, NCT05032157, NCT05030311). There is ongoing phase II research on the efficacy and safety of another BTK inhibitor, rilzabrutinib, in CSU (NCT05107115).

Lirentelimab (AK002)

The transmembrane protein Siglec-8, which plays a regulatory role in intercellular and intracellular signal transduction, is especially expressed in eosinophils and mast cells. Studies have shown that Siglec-8 activation inhibits apoptosis in eosinophils and histamine and prostaglandin release from mast cells [76, 77]. In a phase IIa study with lirentelimab, the response rate at week 22 according to the UCT score was 92% and 36% in omalizumab-naive ($n = 13$) and omalizumab-resistant ($n = 11$) patients, respectively. Response was maintained in the 12-month open-label extension phase of the same trial. No side effects were reported, except for mild-to-moderate infusion reactions [78–80]. A phase II study evaluating the efficacy and safety of lirentelimab therapy is ongoing (NCT05528861).

Reslizumab, mepolizumab, benralizumab

IL-5 plays a major role in the development of eosinophils. Considering the increased number of eosinophils in urticarial lesions and the possible effects of eosinophils on the pathogenesis of CSU via mast cell and coagulation

pathway, IL-5-directed therapies (reslizumab, mepolizumab: anti-IL-5, benralizumab: anti-IL-5R) may be a treatment option [81]. Reslizumab and mepolizumab have been reported to be effective in the treatment of CSU in different case reports [82, 83]. In a single-blinded placebo-controlled study, a complete response was obtained in 5 of 9 CSU patients with benralizumab treatment [84]. Nowadays, its development for CSU indication was stopped.

Several clinical trials evaluating the use of TLL018 (oral JAK1/TYK2 inhibitor), barzolvolimab (anti-receptor tyrosine kinase KIT), and THB001 (oral small molecule inhibitor of KIT) in chronic urticaria are ongoing (NCT05373355, NCT05405660, NCT05368285, NCT05510843).

Unmet needs and conclusions

Acute or chronic, the diagnostic and therapeutic management of urticaria is always a challenge. Although the clinical characteristics of the signs and symptoms, that is, wheal, angioedema, and pruritus, are identifiable through the clinical history and physical examination, the differential diagnosis with other entities is broad, both in the acute forms and in the chronic forms of urticaria. The identification of the trigger or triggers should not be limited to environmental agents since the autoimmune nature of the disease, especially in chronic forms, plays an essential role. Thus, the diagnosis and management of urticaria cannot be limited to the symptomatic treatment of the symptoms using H1-antihistamines and other available drugs without first identifying the type of urticaria that the patient shows. The patient needs to know the nature of the disease, the pathogenic bases of the development of the signs and symptoms, and thus understand what the recommended therapeutic strategy is. All forms of urticaria begin on a specific day in the form of acute urticaria and we still do not know how to predict when the episode that begins in a specific person meets the conditions to have a chronic evolution; this is a matter of study. In any case, the disease by its own character greatly interferes in people's lives, requiring early treatment. For this reason, the expansion of knowledge of urticaria as well as the available therapeutic arsenal is essential.

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Compliance with Ethical Standards

Conflict of Interest
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Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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