5.29 Chronic Urticaria

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Glossary

Acute urticaria Episodic occurrence of wheals or angioedema or both for 6 weeks or less.

Angioedema Swelling due to edema within the deeper dermal layers of the skin or mucous membranes. Angioedema can be asymptomatic, itchy, or cause burning pain. It can take several days to resolve.

Biomarker Measurable indicator linking disease endotype with the phenotype.

Chronic inducible urticaria Chronic urticaria caused by a specific and definite trigger that induces the development of wheals, angioedema, or both. Chronic inducible urticaria is classified according to the relevant trigger.

Chronic spontaneous urticaria Recurrence of wheals for more than 6 weeks without a specific and definite trigger.

Endotype Compilation of disease mechanisms explaining disease expression in groups of patients.

Urticaria Urticaria is a skin condition that manifest with wheals (hives), angioedema, or both.

Wheal Superficial red or pale skin swelling, usually surrounded by erythema, which can persist from a few minutes to days. Wheals are generally very itchy but can also cause a burning sensation.

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Abbreviations

aaCSU Autoallergic chronic spontaneous urticaria
AAS Angioedema activity score
AE-Q$_2$oL Angioedema quality of life questionnaire
aiCSU Autoimmune chronic spontaneous urticaria
ASST Autologous serum skin test
ASU Acute spontaneous urticaria
AU Acute urticaria
C5a Complement 5a
C5aR Complement 5a receptor
CIndU Chronic inducible urticaria
CSU Chronic spontaneous urticaria
CU Chronic urticaria
CU-Q$_2$oL Chronic urticaria quality of life questionnaire
FcεRI High affinity IgE receptor
IgE Immunoglobulin E
MRGPRX2 Mas-related G protein-coupled receptor X2
NSAID Non-steroidal anti-inflammatory drugs
TPO Thyreoperoxidase
UAS Urticaria activity score
UCT Urticaria control test

5.29.1 Introduction

Chronic urticaria (CU) is defined as the recurrence of wheals, angioedema, or both for more than 6 weeks (Zuberbier et al., 2018). CU is a prevalent, difficult-to-treat and disabling condition that leads to substantial impairment in quality of life and significant economic burden (Fricke et al., 2020; Guillen-Aguinaga et al., 2016). The care of patients with CU can be challenging and time-consuming not only for physicians working in the general medicine but also specialists, e.g., dermatologists and allergists. Therefore, the implementation of personalized medicine and awareness of current approaches to the diagnosis and treatment of CU among physicians are crucial for the improvement of CU management. In this context, health care providers should know the CU definition, classification, endotypes, comorbidities and causes, and be familiar with CU diagnostic and treatment algorithms (Zuberbier et al., 2018). Here, we provide an up to date review of these aspects of CU and recent findings that have contributed to our current understanding of this common and debilitating disease.

5.29.2 Definition

Urticaria is defined, clinically, as a disease that presents with wheals, angioedema or both. Wheals (hives, *urticae*) are short-lived superficial skin swellings of variable size. Histologically, wheals in patients with urticaria show edema in the dermis and a sparse and transient inflammatory infiltrate. Wheals are associated with itching or burning and are typically accompanied by flare reactions of the surrounding skin. Wheals resolve spontaneously, in urticaria usually within several hours.

Angioedema is a sudden and deep swelling of the lower dermis and subcutis or the mucosa and submucosa. Angioedema is more pronounced than wheals and can be itchy or painful or asymptomatic. Angioedema is of longer duration and slower resolution than wheals. In patients with urticaria, angioedema usually persists for several hours, but can also last for a few days.

Chronic urticaria (CU) is defined by recurrently appearing signs and symptoms, i.e., wheals, angioedema, or both, for more than 6 weeks. Chronic spontaneous urticaria (CSU), the most common form of chronic urticaria, is defined by wheals and/or symptoms that occur spontaneously, i.e., not prompted by definite triggers. Chronic inducible urticaria (CIndU) and its subforms are defined by wheals, angioedema, or both that occur in response to specific and definite triggers (e.g., cold contact in cold urticaria).

5.29.3 Classification

Urticaria is classified as acute, i.e., acute urticaria (AU), when the occurrence of signs and symptoms lasts for 6 weeks or less and as chronic urticaria (CU) when they continue to occur for longer than 6 weeks. Urticaria is also classified based on whether or not the signs and symptoms develop in response to specific and definite triggers or not. The former is inducible urticaria, the latter is spontaneous urticaria. Both, acute and chronic urticaria are either spontaneous or inducible. Both, spontaneous and inducible urticaria are either acute or chronic. Consequently, urticaria comes as acute spontaneous urticaria, chronic spontaneous urticaria (CSU), acute inducible urticaria, and chronic inducible urticaria (CIndU).

CSU is sometimes further subclassified as CSU with a known cause and CSU of unknown cause. Recently, two CSU endotypes have been proposed, resulting in the classification of CSU as type I autoimmune CSU, type IIb autoimmune CSU, and CSU due to unknown cause. CIndU is further subclassified as physical CIndU and non-physical CIndU. In physical CIndU (sometimes referred to simply as physical urticaria) the specific and definite eliciting trigger is of a physical nature, e.g., cold or heat (cold urticaria, heat urticaria), irradiation with UV light or visible light (solar urticaria), friction (symptomatic dermographism), pressure (pressure urticaria), or vibration (vibratory angioedema). In contrast to these physical forms of CIndU, the development of wheals, angioedema, or both in the other types of CIndU is triggered by non-physical triggers, i.e., by skin contact with urticariogenic substances (contact urticaria), water (aquagenic urticaria), or sweat (cholinergic urticaria). This CIndU is sometimes referred to as chemical CIndU.

5.29.4 Epidemiology

CU is one of the most common skin pathologies. Lifetime prevalence for CSU was reported to be 0.5–2% (Zuberbier et al., 2010). Women are consistently found to be affected twice or three times as often as men (Zuberbier et al., 2010). CSU can occur at any age, but the peak age of disease onset is between 20 and 40 years. This is valid for men and women (Maurer et al., 2011b). The estimated point prevalence of CSU in pediatric patients is around 1% (Balp et al., 2018). CSU may be more common in Asia and South America as compared to North America and Europe, and the prevalence appears to be increasing (Fricke et al., 2020). CSU is held to be at least twice as common as CIndU (Zuberbier et al., 2010).

5.29.5 Pathogenesis

Although urticaria is a common disease, its pathogenesis is not completely understood. Skin mast cells are known to play a central role in driving the development of the signs and symptoms of urticaria. Their activation and subsequent degranulation result in itch, wheals and angioedema formation. Skin mast cells are mainly localized around cutaneous blood vessels and sensory nerves (Siebenhaar et al., 2018), in the upper papillary dermis as well as the deep dermis and subcutis. Histamine, proteases, cytokines, chemokines and other inflammatory mediators released by cutaneous mast cells activate sensory skin nerves (itch, skin burning, and pain), dilate skin blood vessels (erythema, hyperthermia) and induce plasma extravasation (edema and influx of basophils, neutrophils, eosinophils and other immune cells).

Importantly, skin mast cell degranulation in patients with urticaria, in the vast majority of urticaria types and cases, is not due to classical allergic activation where environmental allergens bound to their specific IgE crosslink high affinity IgE receptors on the surface of mast cells. Instead, skin mast cells, in patients with urticaria are most commonly activated by non-allergic mechanisms. In CSU, mast cell degranulation is held to be induced by autoantibodies including IgG and IgM autoantibodies to IgE or its receptor, FcεRI, (Grattan et al., 1991; Hide et al., 1993) and IgE autoantibodies directed against autoantigens (autoallergens) such as thyreoperoxidase (TPO) (Altrichter et al., 2011; Sanchez et al., 2019), double stranded DNA (Hatada et al., 2013), or interleukin-24 (Schmetzer et al., 2018). The latter are indicative of CSU due to autoimmunity type I, i.e., autoallergy and the former of autoimmune type IIb CSU. Up to 80% of patients with CSU exhibit circulating IgE autoantibodies linked to type I autoimmune CSU and up to 60% show type IIb autoimmunity-driving IgG or IgM autoantibodies, suggesting that mast cell activation in some patients with CSU may be due to both, type I and IIb autoimmune mechanisms. Furthermore, a recent study aimed to better define the clinical and immunological features and to explore potential biomarkers of autoimmune CSU (aiCSU) showed that 8% of the patients with aiCSU fulfilled all three criteria of type IIb autoimmunity, namely positive autologous serum skin test (ASST), positive basophil activation/histamine release and high IgG anti-FcεRI/IgE levels (Schoepke et al., 2019).

Autoallergy, i.e., IgE-mediated type I autoimmunity as a mechanism of autoallergic CSU (aaCSU) was first hypothesized following observations of IgE autoantibodies to thyreoperoxidase (Altrichter et al., 2011). High rate of CSU patients with elevated IgE levels and the fast onset of the beneficial effects of omalizumab (anti-IgE) in many CSU patients supports this hypothesis (Metz et al., 2014b). On the other hand, type IIb autoimmunity in CSU was initiated by reports that autologous sera injected intradermally produced a wheal at the site of injection, what is currently known as the ASST (Grattan et al., 1986). Subsequently, studies showing that IgG antibodies to the patient's own IgE or FcεRI were able to cause basophil and mast cell degranulation in vitro, support this hypothesis of type IIb autoimmunity in the pathogenesis of aiCSU (Grattan et al., 1990).

Other mechanisms that impact on skin mast cell degranulation in urticaria are held to include their activation via Mas-related G protein-coupled receptor X2 (MRGPRX2), the complement component 5a receptor 1, cytokine and alarmin receptors. For example, mast cell-activating autoantibodies, when binding to their targets on the mast cell membrane, result in complement activation, and

subsequent C5a formation can lead to further mast cell activation and degranulation after binding to the C5aR (Kikuchi and Kaplan, 2002). In addition, both substance P (Metz et al., 2014a) and its receptor, MRGPRX2 have been found to be upregulated in patients with CSU (Fujisawa et al., 2014).

In addition to mast cells, basophils are also likely to play a role in the pathogenesis of CSU. In some studies, basopenia, i.e., low basophil counts in the peripheral blood, is associated with severe, antihistamine-resistant and autoimmune CSU (Grattan et al., 1997, 2003; Magen et al., 2011). A paradoxical downregulation of FcεRI-mediated, anti-FcεRI/anti-IgE antibody-induced histamine release from basophils is observed during active disease (Cugno et al., 2009; Sabroe et al., 1998; Sterba et al., 2015). In addition, the serum of patients with active CSU exhibits a suppressed basophil FcεRI activity (Sterba et al., 2015). Whether these changes in basophil function are pathogenic or secondary events needs to be further investigated.

Vascular endothelial cells and eosinophils may also play a role in the pathogenesis of CSU. High numbers of tissue factor-expressing cells such as eosinophils are found in the lesional skin of CSU patients, which activate the extrinsic coagulation pathway (Cugno et al., 2009). Activated coagulation factors may induce plasma extravasation followed by degranulation of skin mast cells and edema formation that lead to wheal formation. Furthermore, eosinophils are activated by autoantibodies against the low-affinity IgE receptor (FcεRII), which are detected in about 70% of CSU patients (Puccetti et al., 2005). In addition, eosinopenia is frequently observed in patients with CSU (Altrichter et al., 2020; Kolkhir et al., 2020b). Possible mechanisms include the depletion of blood eosinophils by recruitment into the skin during active disease and immunological destruction in the blood (Staumont-Salle et al., 2006).

5.29.6 Clinical picture

5.29.6.1 Chronic spontaneous urticaria

Patients with CSU can exhibit either wheals (**Fig. 1**) or angioedema (**Fig. 2**) or both symptoms (**Fig. 3**). The pattern of occurrence of wheals and angioedema has been examined in several studies in CSU patients. A representative cross-sectional population-based survey performed in Germany analyzed 4093 men and women of whom 8.8% had any form of urticaria, thus including acute and chronic, and 1.8% had CU. About one third of CU patients developed both, wheals and angioedema. About 61% and 6% of patients experienced solely wheals and solely angioedema, respectively (Zuberbier et al., 2010). A more recent study included 673 patients primarily from hospital-based specialist centers in Canada, France, Germany, Italy, Spain, the Netherlands and the United Kingdom. From these patients 59% had both wheals and angioedema (Maurer et al., 2017a). Another recent study found that 5 in 10 CSU patients had wheals and angioedema, about 1 in 3 CSU patients had only wheals, and 1 in 10 patients had only angioedema (Sussman et al., 2018). In pediatric patients with CSU 5–14% were found to have angioedema (Balp et al., 2018).

Disease activity can change markedly in a patient over time, with asymptomatic periods of several weeks or months and then periods of high disease activity. Some patients report that triggers such as stress or infections, can sporadically lead to the exacerbation of CSU.

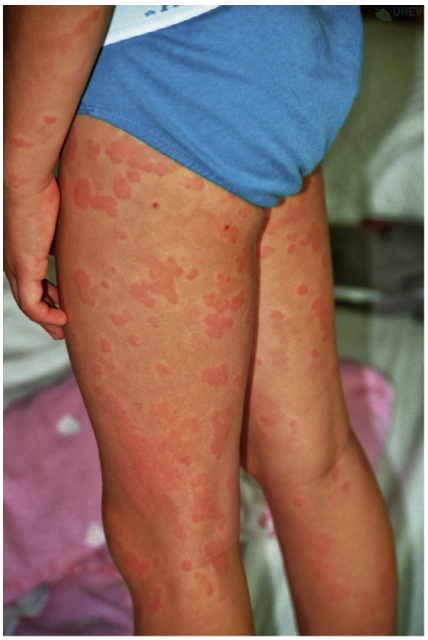

Fig. 1 Clinical picture of a patient with chronic spontaneous urticaria displaying multiple wheals on the legs. https://www.urtikaria.net/en/for-patients/galerie/bilder-upload.html.

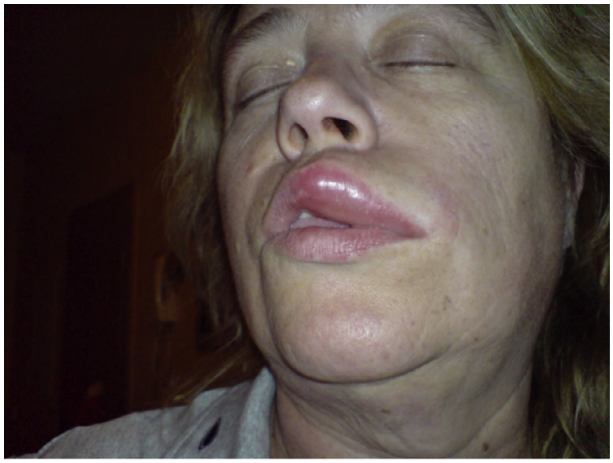

Fig. 2 Clinical picture of angioedema of the upper lip in a patient with chronic spontaneous urticaria. https://www.urtikaria.net/en/for-patients/galerie/bilder-upload.html.

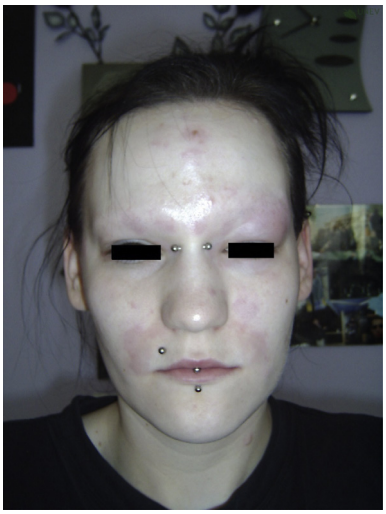

Fig. 3 Clinical picture of a patient with chronic spontaneous urticaria with both, wheals on the face and angioedema of the upper eyelid. https://www.urtikaria.net/en/for-patients/galerie/bilder-upload.html.

The signs and symptoms of CSU can occur at any time of the day but do so most commonly during the evening hours. Wheals can occur anywhere, but favor the arms and legs in most patients (Maurer et al., 2009). Angioedema occurs most commonly on the face (e.g., lips and eye lids) as well as the hands and feet (Zuberbier et al., 2010). In most patients with moderate or severe CSU, wheals and/or angioedema occur on a daily or nearly daily basis (Maurer et al., 2011b).

Few studies investigated the duration of urticaria with different results probably due to differences of subject characteristics. However, these studies clearly show that most of patients suffer for more than 1 year and a considerable proportion suffers for even longer (Maurer et al., 2011b; van der Valk et al., 2002). The average duration of CSU is held to range from 4 to 7 years. CSU shows spontaneous remission in virtually all patients (Maurer et al., 2011a,b; Zuberbier et al., 1996a,b). It is however difficult to predict when spontaneous remission will happen in individual patients. Spontaneous remissions more commonly occur in patients with short duration of CSU, i.e., during the first 2 years, as compared with patients who have CSU for many years.

5.29.6.2 Chronic inducible urticaria

CIndU includes different forms of physical urticaria and non-physical urticaria, i.e., cholinergic urticaria (Fig. 4), contact urticaria and aquagenic urticaria (Table 1). Specific triggers, such as cold in cold urticaria (Fig. 5) or scratching in symptomatic dermographism (Fig. 6), induce wheals and angioedema in patients suffering from CIndU. These triggers are definite triggers, i.e., exposure to the relevant trigger always induces wheals and/or angioedema, and wheals and/or angioedema only occur after trigger exposure.

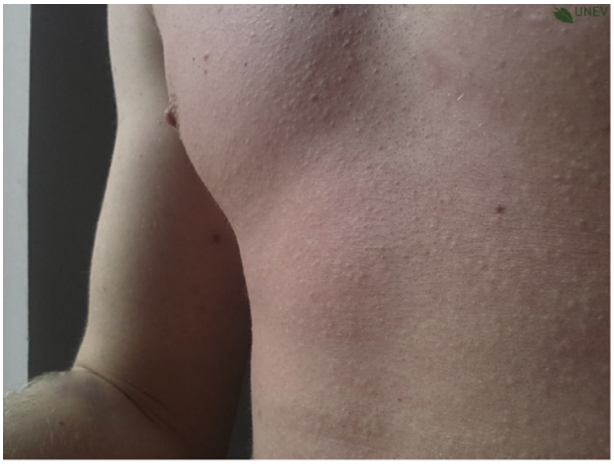

Fig. 4 Clinical picture of a patient displaying the typical small wheals surrounded by erythematous flares of cholinergic urticaria. https://www.urtikaria.net/en/for-patients/galerie/bilder-upload.html.

Table 1 Frequency of different forms of CIndU.

	Frequency	*Synonyms*	*Misnomer*
Physical urticaria			
Symptomatic dermographism	Very frequent	Urticaria factitia, dermographic urticaria	
Cold urticaria	Frequent	Cold contact urticaria, acquired cold urticaria	Cold allergy
Delayed pressure urticaria	Rare	Pressure urticaria	
Solar urticaria	Rare		Sun allergy
Heat urticaria	Very rare	Heat contact urticaria	
Vibration-induced angioedema	Very rare	**Vibratory angioedema**	
Cholinergic urticaria	Frequent		
Contact urticaria	Rare		
Aquagenic urticaria	Very rare		Water allergy

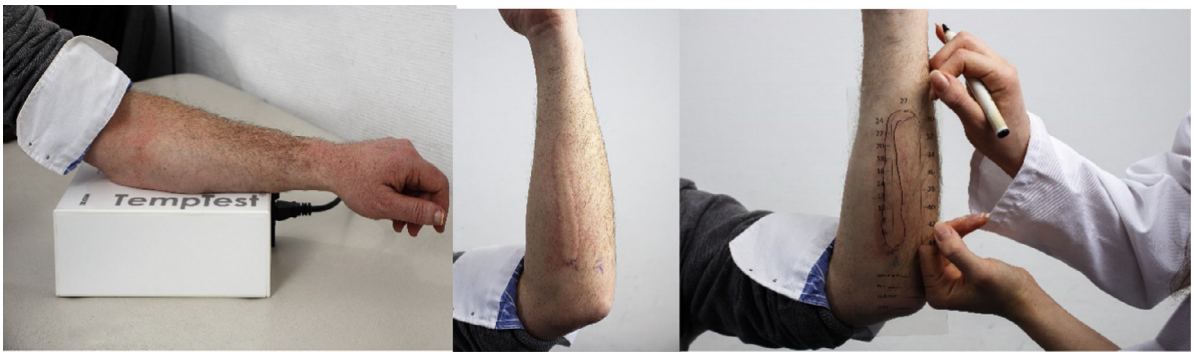

Fig. 5 Clinical picture of a patient with cold urticaria being tested with TempTest®. The patient places the inner forearm on the device for 5 min. TempTest® applies a temperature range from 4° to 44°C, continuously. After 10 more minutes, the cold-induced wheal that has developed on the arm is compared to the stencil to determine the threshold temperature. https://www.urtikaria.net/en/for-patients/galerie/bilder-upload.html.

This makes CIndU a somewhat more predictable disease than CSU in terms of the occurrence of signs and symptoms. In terms of its duration, CIndU is as unpredictable as CSU. There are, currently, no biomarkers or other indicators that can predict, in individual patients, the duration of their CIndU. Like CSU, CIndU goes into remission in all or almost all patients after several years. CIndU is often of longer duration as compared to CSU. The wheals in patients with CIndU are often of shorter duration than the wheals in patients with CSU (Magerl et al., 2016; Maurer et al., 2011b).

In patients with CIndU, high frequency trigger exposure and a low trigger threshold result in high disease activity, i.e., wheals and/or angioedema develop often and are severe. Disease activity is challenging to assess in patients with CIndU, as it also depends on exposure and possible avoidance behavior towards the respective triggers. Validated tools for measuring disease activity in the

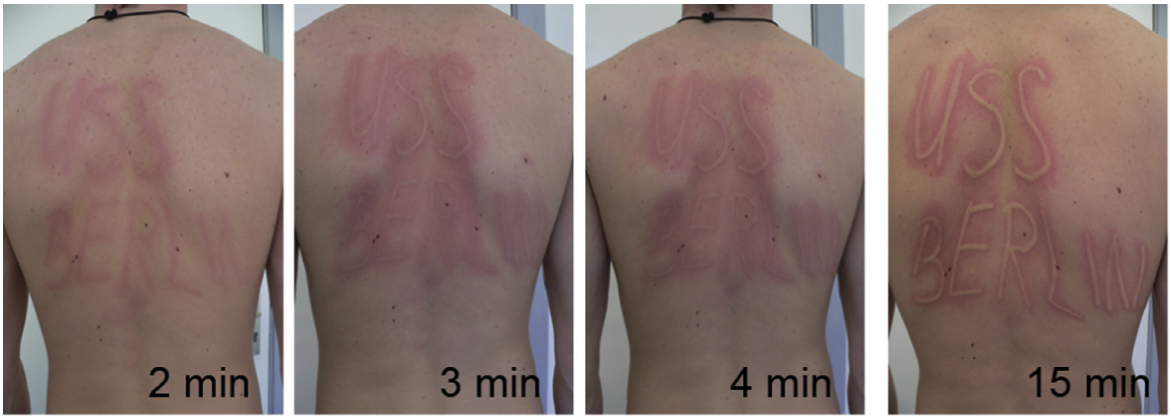

Fig. 6 Clinical picture of a patient displaying symptomatic dermographism. The words were "written" with a pointed object on the back and the writing appears in the form of very itchy wheals. https://www.urtikaria.net/en/for-patients/galerie/bilder-upload.html.

more common forms of CIndU are currently under development according to the guidelines for patient-related outcome measures. Trigger thresholds, i.e., the sensitivity to symptom-inducing triggers, is rather constant in most patients with CIndU. For the description of different provocation tests to measure trigger thresholds, please see our **Section 5.29.7**.

The signs and symptoms of CIndU typically occur where the skin is exposed to the relevant trigger. Skin sites such as the hands and the face, which are exposed to cold and friction and UV light, are more commonly affected. Systemic reactions including anaphylaxis may occur and are held to be due to the effects of histamine and other mediators released by skin mast cells after trigger exposure (Magerl et al., 2016).

5.29.7 Diagnostics

5.29.7.1 Acute spontaneous urticaria

The spontaneous appearance of itchy wheals, angioedema, or both for 6 weeks or less is pathognomonic of ASU. ASU is self-limited, and diagnostic procedures are not usually required and, when performed, often fail to identify the cause. Suspicion of allergy is the only exception. In this case, potentially relevant allergens should be looked for by allergy testing, and patient education can help to avoid subsequent exposure to the causative allergen (Zuberbier et al., 2018).

5.29.7.2 Chronic spontaneous urticaria

CSU patients present with itchy wheals and/or angioedema that develop independently of definite triggers and recur for more than 6 weeks. The diagnostic workup is aimed at the exclusion of differential diagnoses, the identification of comorbidities, the cause of CSU, the characterization of conditions and factors relevant for the course and management of the disease, and the assessment of disease activity, impact and control (**Fig. 7**).

5.29.7.2.1 Exclusion of differential diagnoses

Physicians should first address the possibility that the clinical signs of patients, wheals and angioedema, may be due to other inflammatory conditions including urticarial vasculitis or autoinflammatory syndromes. In this case, clinical signs and symptoms, e.g., wheals of more than 24 hours duration, elevated blood markers of inflammation, e.g., erythrocyte sedimentation rate and C-reactive protein, and skin biopsy (if urticarial vasculitis is suspected) can help to confirm the correct diagnosis.

5.29.7.2.2 Identification of comorbidities

The evaluation for common comorbidities such as depression and anxiety, CIndU, and autoimmune diseases are also relevant in the assessment of patients with CSU due to their high prevalence (Kolkhir et al., 2016b, 2017a,b,c). Comorbid depression and anxiety add to the burden of CSU and the impairment of quality of life due to CSU (Staubach et al., 2011). Concomitant CIndU and autoimmune thyroid disease have been linked to longer CSU duration and progression from ASU to CSU. In some cases, CSU has been reported to show remission or improvement after the treatment of comorbid malignancy, infections or hyper- and hypothyroidism (Kolkhir et al., 2017c, 2018b; Larenas-Linnemann et al., 2018). For all of these reasons, patients with CSU should be assessed for common comorbidities, by targeted questions and, if indicated, subsequent testing (please see **Section 5.29.8**).

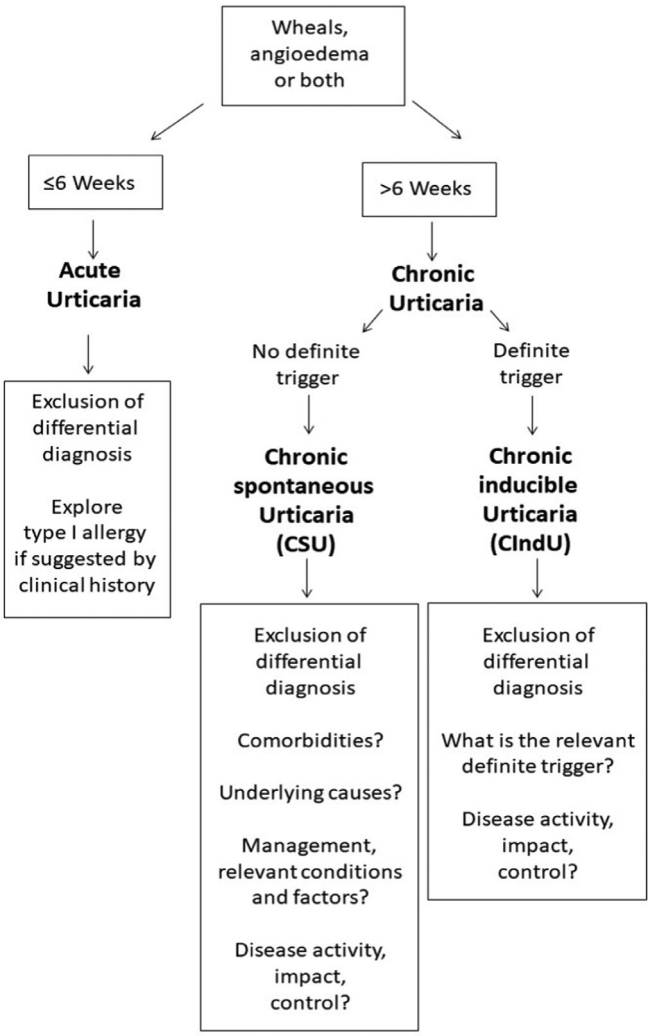

Fig. 7 Diagnostic workup.

5.29.7.2.3 The search for underlying causes

Today, CSU is held to be, in most patients, an autoimmune disease, and two types of autoimmunity are involved. Patients with type I autoimmune (autoallergic) CSU (aaCSU) exhibit IgE autoantibodies to autoallergens such as TPO (Altrichter et al., 2011; Sanchez et al., 2019), double stranded DNA (Hatada et al., 2013), or interleukin-24 (Schmetzer et al., 2018). Patients with aaCSU usually display high normal or elevated IgE levels and respond well to omalizumab treatment (Kolkhir et al., 2017a,b; Maurer et al., 2011a). Commercial assays to detect IgE autoantibodies or auto-IgE are not currently available.

The second is autoimmunity type IIb, with IgG and IgM antibodies to the α-chain of the high affinity IgE receptor, FcεRI, to IgE and maybe to other yet not described targets. The following three diagnostic criteria should be fulfilled in order to establish the diagnosis of type IIb autoimmune CSU (aiCSU): (1) a demonstration of in vivo relevance of autoreactivity: a positive ASST, (2) a demonstration of functionality in vitro: positive basophil tests (basophil histamine release assay, BHRA, or basophil activation test, BAT), and (3) a demonstration of antibody specificity: A positive immunoassay for specific IgG and/or IgM autoantibodies against FcεRI and/or anti-IgE by immunoassays (Konstantinou et al., 2013). These assays require standardized methods to obtain reliable results, which may not be available to most physicians. The ASST is readily accessible to all clinicians; however, one has to be cautious since it may give false-positive results (Kaplan, 2004). The lack of concordance between ASST, histamine release assays, and ELISA/Western blotting to detect IgG anti-FcεRI remains a problem in identifying the proper test to define aiCSU.

In addition, patients with aiCSU usually show high disease activity, high levels of IgG-anti-TPO, low levels of total IgE, poor response to antihistamines and omalizumab and good response to cyclosporine (Gericke et al., 2017; Iqbal et al., 2012; Schoepke et al., 2019). Other markers of aiCSU reported include eosinopenia and basopenia. Basophil reactivity assessed by histamine release is the best predictor for aiCSU (Schoepke et al., 2019).

5.29.7.2.4 Characterization of conditions and factors relevant for the course and management of the disease

A good clinical history is mandatory to explore relevant aggravators and risk factors for a long duration, a severe course, and resistance to treatment of CSU. Based on clues from the history, patients should be further investigated by diagnostic tests if indicated.

In CSU, chronic infections, food intolerance and stress are considered as common aggravating conditions. Diagnostic testing for *Helicobacter pylori*, as well are ruling out recurrent tonsillitis or sinusitis are recommended if indicated by the patients' history. Food intolerance, e.g., intolerance to preservatives or naturally occurring aromatic compounds, has been reported to trigger CSU symptoms in about one out of three patients (Magerl et al., 2010; Zuberbier et al., 1995). The mechanisms of food intolerance are different from those of immediate type I allergic reactions and do not involve sensitization and IgE antibodies to food allergens. If a patient's clinical history is suggestive of food intolerance, pseudoallergen- and histamine-low diets for a maximum of 3 weeks can be considered. Finally, stress is a well-known aggravating factor of CSU and might contribute to higher disease activity (Varghese et al., 2016).

Some additional factors have been associated with the course of disease and response to treatment. Severe CSU and a long time to spontaneous remission have been linked to higher age at onset of CSU, female gender, long CSU duration and NSAID hypersensitivity (Sanchez-Borges et al., 2017). Patients with CSU, who are non-responders to antihistamine treatment, have higher C-reactive protein levels as compared to responders (Kolkhir et al., 2018a). Positive ASST, low levels of total IgE as well as failure of IgE levels to increase after the start of treatment have been reported to predict poor or slow treatment responses to omalizumab (Ertas et al., 2018; Marzano et al., 2019; Nettis et al., 2018; Weller et al., 2018b).

5.29.7.2.5 Assessment of disease activity, impact and control

All patients with CSU should be assessed, at first contact, and monitored for the duration of their CSU for disease activity, impact on quality of life, and disease control (Weller et al., 2015). The urticaria activity score, UAS, is the gold standard for measuring disease activity in patients with CSU (Mlynek et al., 2008). The UAS entails the number of wheals and the intensity of pruritus over the course of 24 hours, usually by once daily documentation by patients. The sum score of the UAS of seven consecutive days is the UAS7 (Hawro et al., 2018; Hollis et al., 2018). The UAS uses a 0–3 point scale for wheals (0 for none, 1 for <20, 2 for 20–50, and 3 for >50) and a 0–3 point scale for pruritus (0 for none, 1 for mild, 2 for moderate, and 3 for intense). Thus, the value of the UAS and UAS7 ranges from 0 (no disease activity) to 6 and 42 (maximum disease activity), respectively. The UAS does not assess angioedema. Thus, in patients with CSU with angioedema, with or without wheals, the angioedema activity score (AAS) should be used to assess disease activity (Weller et al., 2013). The AAS consists of five questions. A score between 0 and 3 is assigned to every answer. The question scores are summed up to an AAS day sum score, 7 AAS day sum scores to an AAS week sum score (AAS7). The minimum and maximum possible AAS scores are 0–15 (AAS day sum score) and 0–105 (AAS7) (Weller et al., 2013). The AAS and AAS7 range from 0 (no disease activity) to 15 and 105 (maximum disease activity), respectively.

The CU-Q_2oL (Chronic Urticaria Quality of Life Questionnaire) and the AE-QoL (Angioedema Quality of Life Questionnaire) are disease-specific tools to assess quality of life impairment in patients with CSU who have wheals and angioedema, respectively (Baiardini et al., 2005; Mlynek et al., 2009; Weller et al., 2012, 2016). In CSU patients and patients with angioedema, disease control is assessed by using the urticaria control test (UCT) and the angioedema control test (AECT), respectively (Weller et al., 2014, 2020). The UCT consists of four items, and it has a defined cut off for "well-controlled" (12 points or more) vs. "poorly controlled" CSU (11 points or less). The AECT cut off value of 10 or more identifies patients with well-controlled angioedema.

5.29.7.3 Inducible urticarias

Similar to the diagnostic workup in patients with CSU, physicians should exclude differential diagnoses, identify and characterize the relevant triggers, and assess disease activity and control (Magerl et al., 2016) (**Fig. 7**). A search for underlying causes is not recommended as these are currently not known.

5.29.7.3.1 Exclusion of differential diagnoses

Physicians should rule out skin conditions that might mimic signs and symptoms of CindU. Mastocytosis must be excluded in patients with symptomatic dermographism by eliciting the Darier's sign. Similarly, familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS) which belong to the cryopyrin-associated periodic syndromes (CAPS) must be considered in patients with cold urticaria. However, these patients are characterized by the development of symptoms induced by a generalized exposure to cold appearing during the first months of childhood. Polymorphous light eruption should be excluded in patients with solar urticaria. Furthermore, exercise-induced urticaria/anaphylaxis or food or drug-dependent exercise-induced anaphylaxis are important differential diagnosis of cholinergic urticaria.

5.29.7.3.2 The identification and characterization of relevant triggers

The relevant triggers for the development of signs and symptoms in patients with CIndU are explored by provocation and threshold testing, based on the history.

Provocation tests for symptomatic dermographism, formerly called urticaria factitia, are done by stroking the skin with a smooth and blunt object such as a closed ballpoint pen or, preferably, a dermographometer (Magerl et al., 2016; Schoepke et al., 2015). Two types of dermographometers are available: the FricTest® (Moxie, Berlin, Germany) which simultaneously tests four defined trigger strengths and a pen shaped dermographic tester with a spring-loaded tip is used to test individual triggers strengths (HTZ Limited,

Vulcan Way, New Addington, Croydon, Surrey, United Kingdom). Both dermographometers are used vertically across the skin test site for the provocation test. A positive test is defined by the development of an itchy wheal at the provocation site within 10 min. Positive provocation tests should be follow up by threshold testing (Magerl et al., 2016). Provocation tests are useful to monitor disease activity, response to treatment, and disease control.

Provocation test for pressure urticaria and threshold testing is done with weighted rods or a dermographic tester, and the test result is considered to be positive when a red palpable swelling is present 6 h after testing. Delayed pressure urticaria is characterized by erythematous angioedema-like swellings, not wheals, hours after exposure to pressure. These swellings typically persist for several hours or several days.

Provocation testing for vibratory angioedema can be done with a laboratory vortex mixer for 10 min. Skin exposure to vibration is the relevant trigger, and this results in cutaneous swellings or redness that occur within minutes after vibration.

Provocation testing for cold urticaria is done with a melting ice cube in a thin plastic bag, and the test is considered positive when the test site shows a palpable wheal. Patients with cold urticaria should be evaluated for their individual temperature and/or stimulation time thresholds, for example by using a TempTest® instrument (Courage and Khazaka, Köln, Germany) (Magerl et al., 2015, 2016, Maurer et al., 2018a,b,c,d) (**Fig. 5**). Threshold measurements and use of the UCT at every visit allow patients and physicians to monitor disease activity, the therapeutic response, and disease control.

Provocation testing for heat urticaria is done by applying temperatures of up to 44 °C to the skin, for example by TempTest® or metal/glass cylinders filled with hot water. Patients with heat urticaria show whealing after provocation testing and should be assessed for their temperature thresholds to determine and monitor disease activity.

Provocation testing for solar urticaria is done with solar simulators or monochromators, and the test result is positive when a palpable wheal develops. Patients should be threshold tested for their lowest urticaria-triggering dose of radiation.

Provocation testing for cholinergic urticaria is done by first subjecting patients to moderate physical exercise to make them sweat. When this test is positive, patients are exposed in a second test to a warm bath, which also leads to whealing in cholinergic urticaria patients, but not in patients with exercise-induced anaphylaxis. Threshold testing is done by pulse-controlled ergometry.

5.29.7.3.3 Assessment of disease activity, impact and control

In addition to threshold testing, disease activity in patients with CIndU is assessed by the use of disease activity score. Similar to the UAS7, the cholinergic activity score (CholUAS) allows to assess disease activity in patients with cholinergic urticaria. The CholUAS uses a 0–3 point scale for wheals (0 for none, 1 for mild, 2 for moderate, and 3 for intense) and a 0–3 point scale for pruritus (0 for none, 1 for mild, 2 for moderate, and 3 for intense) as well as the exposure and the intensity of elicitors. The disease-specific disease activity score CholUAS7 is calculated as the 7-day sum of [(Whealday + Itchday) × Intensity of elicitor day]. Furthermore, the cholinergic urticaria quality of life questionnaire (CholU-QoL) is a 28-item questionnaire, which is easy and fast to complete for patients and assesses five domains of quality of life such as emotions, symptoms, therapy, functional life, social interaction (Ruft et al., 2018). The CholU-QoL instrument is an specific QoL measure in the field of chronic inducible urticarias that improves routine patient management. In addition, disease activity and quality control scores to assess patients with CIndU are currently under development.

Disease control is assessed by use of the UCT, a 4-item questionnaire with a recall period of 4 weeks to assess disease control in patients with CindU. Each UCT item has five answer options (0–4 points). Accordingly, the UCT total score ranges from 0 to 16 points. Low points indicate high disease activity and poor disease control, whereas higher values are indicative for higher levels of disease control.

5.29.8 Comorbidities

5.29.8.1 Comorbidities of acute spontaneous urticaria (ASU)

ASU can appear in combination with other allergic diseases and wheals can be a "symptom" of allergy such as food and drug allergy or anaphylaxis. For example, in a population-based study examined 4076 children, ASU was significantly associated with allergic diseases, namely asthma, allergic rhinitis and atopic dermatitis, and parental history of allergy (Lee et al., 2017).

Acute infection is thought to be a concurrent disease and/or cause of ASU in a subpopulation of ASU patients (Zuberbier et al., 1996a; Imbalzano et al., 2020; Aoki et al., 1994). In this context, some infections, e.g., upper respiratory tract infections or herpes infections, are more frequently reported in children with ASU, and other infections, e.g., hepatitis virus infections, would appear to be more common in adults with ASU (Imbalzano et al., 2020; Scully and Ryan, 1993; Marrouche and Grattan, 2012). ASU, when linked to an infection, often disappears after remission or eradication of the infection (Imbalzano et al., 2020; Aoki et al., 1994). Recently, ASU has been described to be linked to infections with Dengue virus and SaRS-CoV-2 infection and COVID-19 (van Damme et al., 2020).

5.29.8.2 Comorbidities of chronic spontaneous urticaria

CSU often coexists with other diseases, i.e., comorbidities. Some comorbidities, for example autoimmune thyroiditis, show prevalence rates of up to 30% in patients with CSU and CSU patients may benefit from screening for these conditions (Confino-Cohen et al., 2012; Kolkhir et al., 2017a). Many comorbidities, e.g., depression and anxiety or chronic inducible urticaria (CIndU), add to

the burden of disease and quality of life impairment in patients with CSU. Furthermore, some diseases may be markers of longer CSU duration, e.g., CIndU, and progression from acute spontaneous urticaria to CSU, e.g., Hashimoto's thyroiditis (Kozel et al., 2001; Hiragun et al., 2013; Curto-Barredo et al., 2018; Gregoriou et al., 2009; van der Valk et al., 2002; Magen et al., 2016; Eun et al., 2019). Finally, certain comorbidities may share pathogenic mechanisms with CSU, that supported by CSU remission or improvement after the treatment of malignancy, infection and hyper- and hypothyroidism (Larenas-Linnemann et al., 2018; Kolkhir et al., 2017c; Wedi et al., 2009).

Comorbid CIndU occurs in 11–75% of CSU patients, with most studies reporting rates of >20% (Curto-Barredo et al., 2018; Kozel et al., 2001; Barlow et al., 1993; Sanchez et al., 2017; Silpa-Archa et al., 2011; Juhlin, 1981; Hiragun et al., 2013; Maurer et al., 2017c). Most common comorbid CIndU are symptomatic dermographism (5–75%), delayed pressure urticaria (2–37%), cholinergic urticaria (2–18%), and cold urticaria (1–13%). Several types of CIndU can appear in the same CSU patient (Sanchez et al., 2017). The presence of CIndU in CSU patients is likely to be linked to a longer CSU duration (Curto-Barredo et al., 2018; Kozel et al., 2001), higher CSU disease activity (Curto-Barredo et al., 2018), and a poor response to antihistamine treatment (Curto-Barredo et al., 2018; Magen et al., 2011; Maurer et al., 2017c; Amin et al., 2015). Importantly, improvement of CSU and concomitant CIndU in the same patient can be seen with a similar therapy, e.g., antihistamines and omalizumab (Kocaturk et al., 2017; Maurer et al., 2018d; Zuberbier et al., 2018).

Depression and anxiety are considered important comorbidities of CSU and present in 3–40% and 5–30% CSU patients, respectively (Curto-Barredo et al., 2018; Ozkan et al., 2007; Staubach et al., 2011; Zazzali et al., 2012; Juhlin, 1981; Maurer et al., 2017c). Population-based studies reported that chronic urticaria is associated with a significantly increased risk of mental disorders, mostly depression and anxiety (Chu et al., 2017; Lapi et al., 2016). Although no correlations were found between comorbid psychiatric diagnoses and CSU severity or duration (Ozkan et al., 2007; Herguner et al., 2011; Engin et al., 2008; Chung et al., 2010), the presence of psychiatric comorbidity in patients with CSU is associated with significantly increased quality of life impairment (Staubach et al., 2006; Engin et al., 2008).

CSU patients have an increased risk of developing autoimmune diseases, especially middle-aged female patients with a positive family history for autoimmune disease (Kolkhir et al., 2017a). The most frequent autoimmune comorbidity in CSU is Hashimoto's thyroiditis (also known as autoimmune thyroiditis, ≥5%), pernicious anemia (≥5%), and vitiligo (≥3%) (Maurer et al., 2017c; Kolkhir et al., 2017a,c). In some patients, CSU is a part of "autoimmune polyglandular syndrome," i.e., it occurs in combination with Hashimoto's thyroiditis and other autoimmune diseases. For example, 2% of CSU patients have Hashimoto's thyroiditis and vitiligo, rheumatoid arthritis or pernicious anemia (Kolkhir et al., 2017a). Thyroid autoimmunity is linked to the progression of acute spontaneous urticaria toward CSU (Magen et al., 2016). Therefore, in CSU patients with elevated IgG anti-thyroid antibodies, especially IgG-anti-TPO, and/or risk for autoimmune thyroid diseases, annual reassessment of thyroid function may be warranted (Kolkhir et al., 2017c). In hypo- and hyperthyroid CSU patients, treatment with levothyroxine or anti-thyroid drugs, respectively, may improve CSU symptoms (Kolkhir et al., 2017c).

The prevalence and relevance of comorbid bacterial infections in CSU are still ill characterized, and the results of studies are controversial. A meta-analysis reported a significant, though weak association of *Helicobacter pylori* infection with an increased risk of CSU (Gu et al., 2015). Two of three placebo-controlled, double blind trials linked treatment of *Helicobacter pylori* infection to CSU improvement (Pawłowicz et al., 2018; Gaig et al., 2002; Schnyder et al., 1999). In contrast, a GRADE-based review concluded that "evidence that *Helicobacter pylori* eradication leads to improvement of chronic urticaria outcomes is weak and conflicting" (Shakouri et al., 2010).

Focal bacterial infections have been reported in up to 50% of CSU patients (Hellgren and Hersle, 1964; Buss et al., 2007; Sackesen et al., 2004; Wedi et al., 1998) including sinusitis, dental infection, tonsillitis, urinary infection, and lung infection (Buss et al., 2007; Hellgren and Hersle, 1964; Liutu et al., 1998; Zingale et al., 2006; Wedi et al., 1998; Sackesen et al., 2004). In some of these reports, CSU cleared or improved after appropriate treatment of focal infection, e.g., teeth extraction or antimicrobial therapy.

Parasitic infection is not a frequent comorbidity of CSU in many parts of the world. However, urticaria including CSU can be seen at least in every tenth patient with parasitic infection. The most frequently reported parasites in the context of urticaria are protozoa, primarily *Gardia spp*. and *Blastocystis hominis*, and helminths, mostly *Anisakis simplex*, *Strongyloides stercoralis*, and *Toxocara canis*. In a systematic review, improvement of urticaria was seen in 36% of 269 CSU patients after the treatment of confirmed parasitic infection with antiparasitic drugs. Interestingly, urticaria improved in 97% of 88 patients with previously diagnosed parasitic infection after treatment with antiparasitic drugs (Kolkhir et al., 2016a).

CSU is unlikely to be associated with an increased risk of viral infections, e.g., viral hepatitis and HIV infection (Kolkhir et al., 2018b; Lapi et al., 2016). If patients with recurrent whealing are diagnosed with viral hepatitis, urticarial vasculitis should be excluded (Kolkhir et al., 2018b).

In some patients with CSU, hypersensitivity to *Candida albicans*, *Trichophyton* spp. or *Saccharomyces cerevisiae* was shown by positive skin tests and/or IgE antibodies against fungal antigens. However, the clinical relevance of fungal infection in CSU is still unknown, and antifungal treatment yielded controversial effects on CSU symptoms (James and Warin, 1971; Tang et al., 2003; Doeglas, 1975).

The prevalence of allergic diseases in CSU is 7–59% (Shalom et al., 2017; Chiu et al., 2018; Zazzali et al., 2012; Augey et al., 2008; Sibbald et al., 1991; Chung et al., 2016) and is likely to be quite similar to that in the general population (Sibbald et al., 1991). Some experts and reports support the notion that CSU more often affects atopic patients (Nassif, 2007; Bingefors et al., 2013; Olze and Zuberbier, 2011; Chung et al., 2016), whereas other studies argue against a link between chronic urticaria and atopic diseases (Augey et al., 2008, 2011).

Type I hypersensitivity to environmental allergens is considered a rare cause of chronic urticaria if daily symptoms are present but may be suspected in patients with intermittent symptoms and a temporal relationship to a particular trigger, by either ingestion or contact (Zuberbier et al., 2018). Noteworthy, CSU-approved treatment, antihistamines and omalizumab, can help to diminish the symptoms in patients with CU and concomitant allergic asthma (Normansell et al., 2014) and probably other allergic diseases.

Cancer has been reported in 0–9% patients with CSU (Wedi et al., 1998; Kozel et al., 1998; Kolkhir et al., 2018a; Chen et al., 2012; Lindelof et al., 1990; Karakelides et al., 2006), mostly nonhematologic cancers (Karakelides et al., 2006; Chen et al., 2012). Whether CSU patients have a higher risk of developing cancer is still a matter of debate (McWhorter, 1988; Lapi et al., 2016; Chen et al., 2012; Lindelof et al., 1990; Vena et al., 1985). Cancer can, though rarely, be a cause of CSU, and CSU can resolve with cure of cancer (Larenas-Linnemann et al., 2018; Kolkhir et al., 2018c). According to Curth's criteria, CSU can be considered to be paraneoplastic if the following two major criteria are met: (1) CSU and malignancy appear at approximately the same time, and (2) both conditions follow a parallel course (Curth, 1976). As of now, only 26 cases of urticaria including 17 cases of chronic urticaria were reported to be causally associated with malignancy. In 68% of these patients, urticaria appeared 2–8 months before the malignancy was diagnosed. Resolution of urticaria was seen in all patients after the cure of the cancer (chemotherapy or resection) within days to a few weeks (Larenas-Linnemann et al., 2018).

There is an increasing body of evidence that CSU is associated with metabolic syndrome, which includes central obesity, dyslipidemia, hyperglycemia, and hypertension. Components of metabolic syndrome are prevalent in up to 25% subjects in the general population and considered to be major, modifiable risk factors for atherosclerosis, cardiovascular diseases and diabetes (Alberti et al., 2006). Several large population-based studies demonstrated significantly higher prevalence of components of metabolic syndrome in patients with chronic urticaria as compared to controls (Shalom et al., 2018; Chung et al., 2016; Chang et al., 2016; Lapi et al., 2016). CSU patients had a 1.4-fold greater risk of developing subsequent hypertension (Chang et al., 2016) and the risk of developing CSU was significantly higher in obese subjects (Lapi et al., 2016). Some but not all studies reported an association between the presence of components of metabolic syndrome and chronic urticaria characteristics, e.g., higher disease severity (Ye et al., 2013) and longer duration of CSU (Nebiolo et al., 2009; Zbiciak-Nylec et al., 2018).

5.29.8.3 Comorbidities of chronic inducible urticaria

Not much is known about the comorbidities of CIndU. In patients with both CIndU and CSU, the spectrum of comorbidities can be expected to be similar to that described for CSU. Further studies are needed to better characterize comorbid diseases in patients with isolated CIndU.

5.29.9 Therapy

5.29.9.1 Acute spontaneous urticaria

ASU is usually self-limiting. Therefore, the therapeutic approach includes avoidance of the exposure to suspected triggers and symptomatic treatment to control the symptoms of ASU until the disease resolves by itself. In patients with minimal symptoms or mild ASU, no treatment or a second generation non-sedating H_1-antihistamine should be used. In patients with moderate or severe CSU, a higher than standard H_1-antihistamine dose and/or a short course of systemic glucocorticosteroids should be considered (Zuberbier et al., 2018).

5.29.9.2 Chronic spontaneous urticaria

In CSU, the treatment is prophylactic and aims to provide complete control the development of signs and symptoms, i.e., itchy wheals and/or angioedema. Patient-reported outcome measures such as UAS7, AAS, UCT and AECT can help and should be used to assess and monitor treatment response. The overall goal of treatment is to help patients achieve complete control of their disease, the absence of signs and symptoms of their CSU.

The current global urticaria guideline recommends the use of a second generation H_1-antihistamine at standard dose as the first-line treatment for CSU (Zuberbier et al., 2018). If CSU persists after 2–4 weeks despite this treatment, the second generation H_1-antihistamine should be used at a higher than standard dose (up to four times the standard dose) as the second-line treatment. This approach is effective in some patients, and it is safe and usually well tolerated (Gimenez-Arnau et al., 2009; Staevska et al., 2010; Weller et al., 2018a).

Some CSU patients who are non-responders to antihistamine treatment benefit from add-on omalizumab 300 mg every 4 weeks, the third-line treatment. Omalizumab is a monoclonal anti-IgE antibody, which is approved in many countries and is an effective and safe treatment for CSU (Gimenez-Arnau et al., 2016; Zhao et al., 2016). Patients should be checked for a possible spontaneous remission of their CSU every 6–12 months, if their urticaria is completely controlled with omalizumab treatment. Omalizumab up-dosing in CSU patients (>300 mg/monthly) and treatment of children younger than 12 years, though suggested to be effective and safe by real world evidence, is currently off-label, and further studies on this are needed and should be performed (Türk et al., 2020). There is increasing evidence that omalizumab is more effective in non-type IIb autoimmune CSU.

Cyclosporine is the fourth-line treatment for omalizumab-resistant CSU (Zuberbier et al., 2018). There is increasing evidence that it is more effective in type IIb autoimmune CSU (Kulthanan et al., 2019).

Several new promising treatment options are currently being studied in clinical trials of CSU. These include ligelizumab, a novel anti-IgE monoclonal antibody with a 40- to 50-fold greater affinity to IgE compared with omalizumab (Gasser et al., 2020; Maurer et al., 2019). In fact, after 12 weeks of treatment, ligelizumab 240 mg given every 4 weeks controlled symptoms in 51% of CSU patients as compared with 26% of omalizumab-treated patients, in a recent study (Maurer et al., 2019). Other promising drugs are interleukin 5- and 4/13-targeted monoclonal antibodies, lirentelimab, a monoclonal antibody to Siglec-8, anti-CD200R, as well as fenebrutinib and remibrutinib, Bruton's tyrosine kinase inhibitors (Kolkhir et al., 2020a).

5.29.9.3 Chronic inducible urticaria

As in the case for CSU, the aim of treatment of CIndU is complete disease control until spontaneous remission occurs. To achieve this, the management of CIndU includes avoidance of relevant triggers and treatments that prevent the development of wheals and angioedema. For example, to not wear tight-fitting shoes can help to prevent the development of the signs and symptoms of delayed pressure urticaria. Patients with cholinergic urticaria can benefit from avoidance of offending stimuli such as physical exercise and/or intake of hot or spicy food. In all cases, the thresholds of causative triggers should be assessed to document disease activity and control of CIndU and the response to treatment (Zuberbier et al., 2018).

In CIndU, the first and second steps of treatment are the same as in CSU, i.e., a second generation non-sedating H_1-antihistamine at standard and up to four times the standard dose, respectively (Dressler et al., 2018; Maurer et al., 2018c). The use of a higher than standard-dosed antihistamine allows for better prevention of CIndU signs and symptoms as compared to standard-dosed treatment (Abajian et al., 2016; Krause et al., 2013; Magerl et al., 2012). In patients with some subtypes of CIndU, e.g., cold urticaria, short term prophylactic treatment may be considered if exposure to the trigger, e.g., cold, is planned (Zuberbier et al., 2018). In patients who fail to respond to antihistamine treatment, omalizumab therapy should be initiated. Although off-label, results of controlled trials and real world data support its use in CIndU (Maurer et al., 2017b, 2018d; Metz et al., 2017).

In omalizumab non-responder patients with CIndU, several other therapies such as cyclosporine A should be considered. All of these treatments are off label and the evidence in support of their use is limited. Patients with cold urticaria may benefit from doxycycline treatment (Gorczyza et al., 2017). Other treatment options include afamelanotide, an analog of α-melanocyte-stimulating hormone, for solar urticaria (Haylett et al., 2011), UVB therapy for symptomatic dermographism (Borzova et al., 2008), reslizumab, an interleukin-5 antagonist monoclonal antibody (Maurer et al., 2018a), or anti-TNFα (Magerl et al., 2007) in delayed pressure urticaria. Clotiazepam, an anxiolytic benzodiazepine, and propranolol, a beta blocker, were effective in a refractory case of adrenergic urticaria (Kawakami et al., 2015) and in a patient with cholinergic urticaria (Ammann et al., 1999), respectively. Desensitization to the offending stimulus has been described in solar urticaria, cold urticaria, heat urticaria and cholinergic urticaria (Minowa et al. 2020). Although this treatment might be useful in patients with resistant CIndU, it requires daily exposure of patients to their specific trigger. This can decrease patients' quality of life and lead to poor patient compliance. There is an urgent medical need for new and approved drugs for this indication.

See Also: 5.17: Eosinophils, Mast Cells and Basophils; 5.22: Biologics Targeting Immune Modulation in Inflammatory Disorders; 5.28: The Pharmacology of Antihistamines

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