The Classification, Pathogenesis, Diagnostic Workup, and Management of Urticaria: An Update

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Abstract

Wheals and angioedema are the signature signs of urticaria, and itch is the key symptom. Urticaria, in most patients, is acute and resolves within days (acute urticaria, AU). Chronic urticaria (CU) can be of long duration and results not only in severely impaired quality of life but also has a socioeconomic impact due to work productivity impairment. In some patients with CU, the wheals and angioedema are induced exclusively by defined and definite triggers (chronic

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inducible urticaria, CIndU). In most patients with CU, wheals and angioedema develop unprompted, spontaneously (chronic spontaneous urticaria, CSU). The management of CU aims for the complete control and absence of its signs and symptoms. This is achieved, in most patients, by prophylactic treatment until spontaneous remission occurs. Modern, second-generation H1-antihistamines are the first-line therapy, with the option of updosing to fourfold, and omalizumab is used when this fails.

Keywords

Angioedema · Chronic · Hives · Inducible · Itch · Mast Cell · Pruritus · Spontaneous · Urticaria · Wheals

1 Definition

Urticaria is a mast cell-mediated condition characterized by itchy wheals, angioedema, or both (Church et al. 2018; Zuberbier et al. 2018). The wheals in patients with urticaria are short-lived transient superficial itchy skin swellings. Initially pale in color (Fig. 1), they progressively take on a reddish hue and develop a surrounding flare (erythema, Fig. 1) and then resolve fully over the course of minutes to hours without obvious subsequent skin alterations. Wheals in patients with urticaria are usually itchy, but may also come with skin burning, pain, or stinging. Angioedema is a rapid swelling of the dermis and subcutis or of the mucosa and submucosa (Fig. 1). Angioedema in patients with urticaria most commonly occurs in the face (lips, eyes), and it does not occur in the gastrointestinal tract or the airways.

2 Classification

Urticaria is commonly classified, based on its duration, as acute and chronic. In acute urticaria (AU), wheals and/or angioedema occur for less than 6 weeks. In chronic urticaria (CU), wheals and/or angioedema occur for more than 6 weeks (Zuberbier et al. 2018). Urticaria is further subclassified as spontaneous or inducible. In patients with spontaneous urticaria, acute or chronic, the development of wheals and angioedema is unprompted and unpredictable. In patients with inducible urticaria, wheals and/or angioedema occur only in response to specific and definite triggers acting on the skin (Magerl et al. 2016) (Fig. 2). These triggers can be physical stimuli, in forms of physical urticaria, or urticariogens, for example in contact urticaria and aquagenic. The triggers of physical urticaria include skin exposure to cold and heat (cold urticaria, heat urticaria), friction, pressure and vibration (symptomatic dermographism, pressure urticaria, vibratory angioedema), and ultraviolet or visible light (solar urticaria). In patients with cholinergic urticaria, symptoms are triggered by exercise or passive warming (e.g., hot showers, exercise, spicy food). Some patients have more than one subtype of urticaria, for example chronic spontaneous urticaria (CSU) together with symptomatic dermographism.

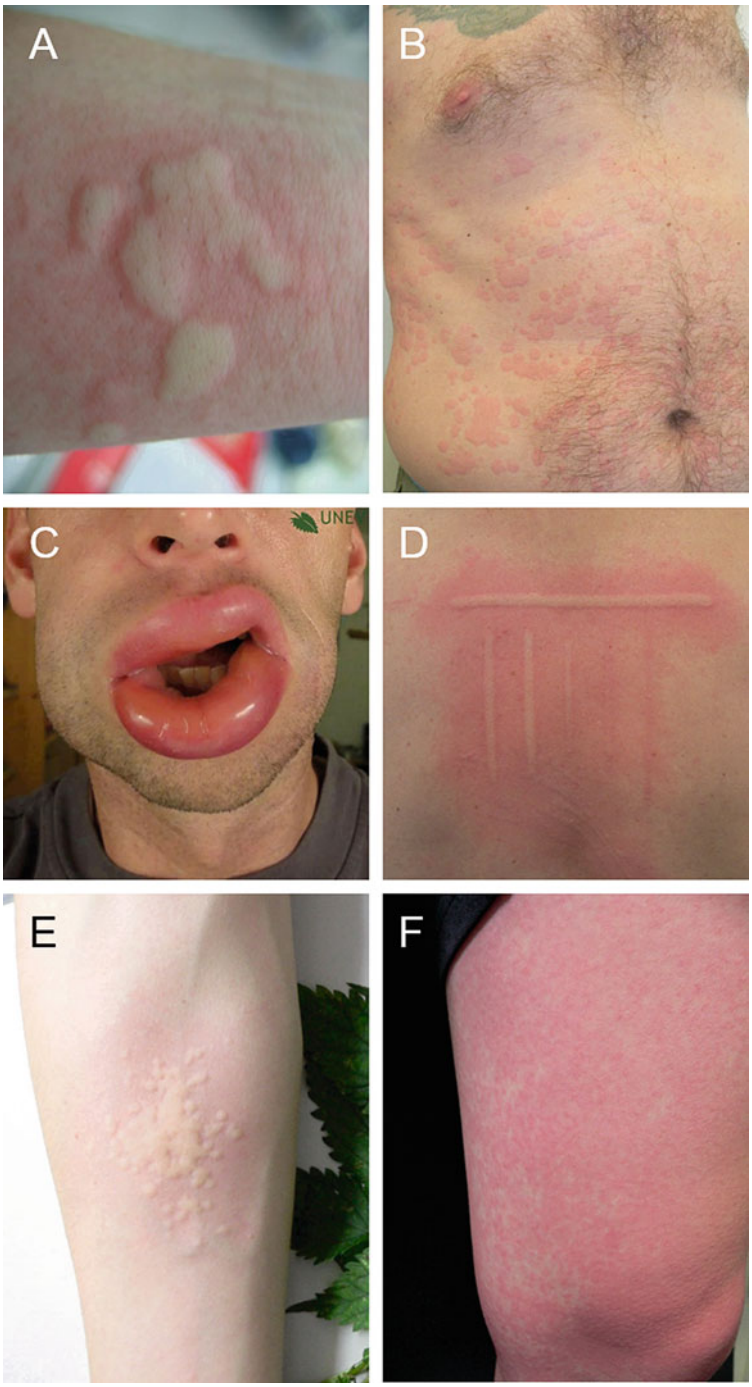

Fig. 1 Wheals and angioedema in urticaria. (**a**) Wheals at an early stage of development in a patient with chronic spontaneous urticaria. (**b**) Wheals of several hours duration in a patient with chronic spontaneous urticaria. (**c**) Angioedema in a patient with chronic spontaneous urticaria. (**d**)

3 Epidemiology

Urticaria is a very common condition, experienced by virtually everyone, at one point during his or her life, as acute urticaria or after touching urticariogenic plants such as stinging nettles or animals, for example jellyfish (Fig. 1). The lifetime prevalence of acute spontaneous urticaria is estimated to be up to 20% (Maurer et al. 2011a; Zuberbier et al. 2010). Urticaria, in patients with acute spontaneous urticaria, rarely progresses to CSU. Acute inducible urticaria is rare. CSU, which is held to be at least twice as common as CIndU, has an estimated point prevalence of 1%, in both children and adults (Maurer et al. 2011a; Balp et al. 2018). CSU can occur at any age and often starts between the 20th and the 40th year of life. Women are affected twice or three times as often as men (Maurer et al. 2011a; Siebenhaar et al. 2018).

4 Pathogenesis

Urticaria is a mast cell-driven disease, i.e. in all patients with urticaria, the wheals and angioedema are due to the degranulation of skin mast cells and the effects of histamine and other proinflammatory mediators released by this process (Church et al. 2018). Skin mast cells are mainly localized around cutaneous blood vessels and sensory nerves (Siebenhaar et al. 2018), in both the upper papillary dermis and the deep dermis and subcutis. When mast cells are triggered to degranulate, they discharge cytoplasmic granules. These granules contain histamine, proteases, and other mediators of inflammation that activate sensory skin nerves (itch, skin burning, pain), dilate skin blood vessels (erythema, hyperthermia), and induce plasma extravasation (edema and influx of basophils, neutrophils, eosinophils, and other immune cells). The action of histamine on its H_1 receptor plays a crucial role in the development of urticaria signs and symptoms. Following their degranulation, skin mast cells produce and secrete prostaglandins, leukotrienes, and platelet activating factor as well as several cytokines. These mediators, together with infiltrating immune cells, are held to contribute to the inflammatory response induced by degranulation and to prime the skin including skin mast cells for subsequent whealing and angioedema formation.

In patients with CSU, the degranulation of skin mast cells is not due to classical allergic activation, i.e. the binding of environmental allergens to specific IgE bound to cell surface IgE receptors. Instead, mast cells are degranulated by autoantibodies including IgG 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),

Fig. 1 (continued) Wheals induced by scratching of the skin, in a patient with symptomatic dermographism. (**e**) Wheals induced by skin contact with a stinging nettle (contact urticaria). (**f**) Wheals with pronounced erythema, in a patient with cholinergic urticaria

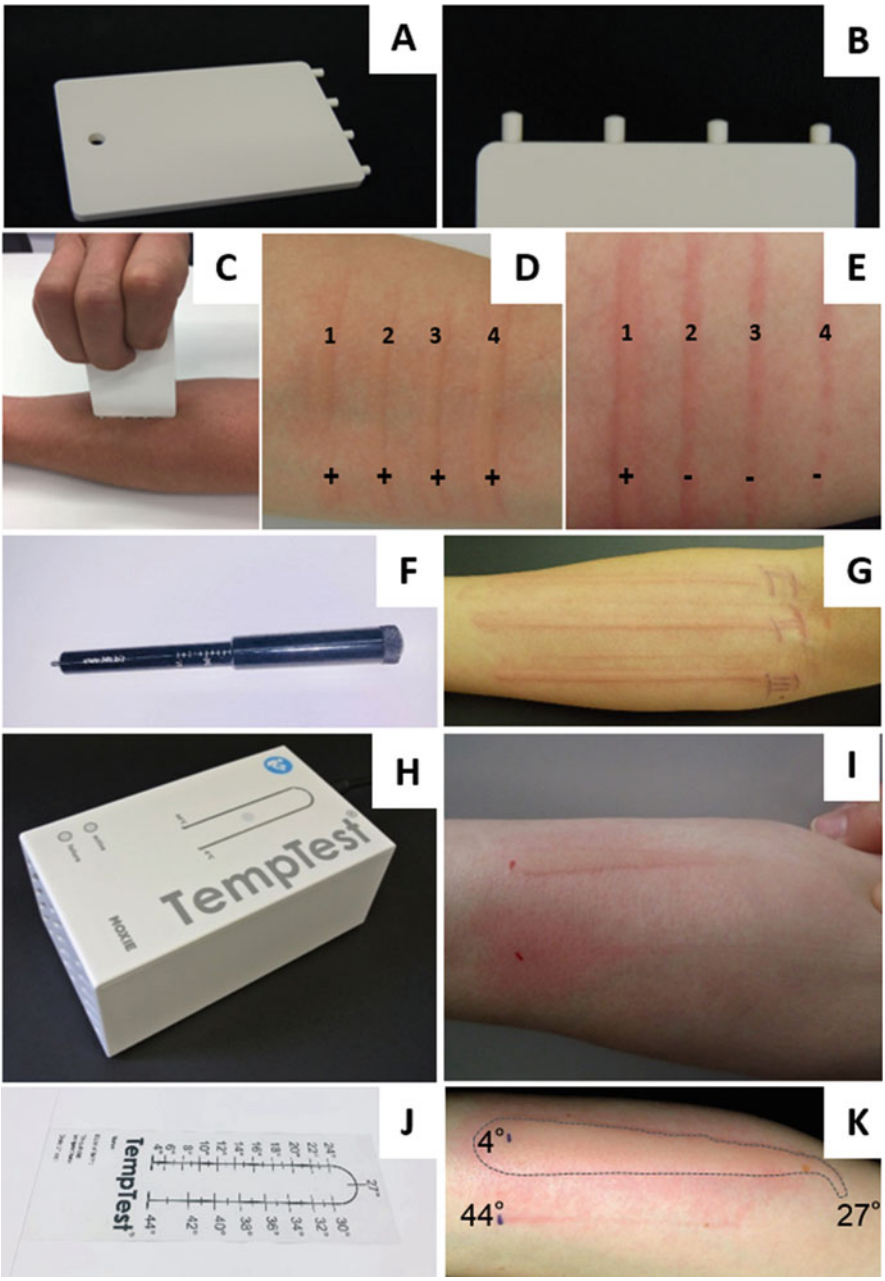

Fig. 2 Provocation and threshold testing in patients with chronic inducible urticaria. FricTest® (**a**–**c**) is a dermographometer used for provocation testing and threshold testing in patients with symptomatic dermographism. The instrument has four pins of different lengths (**b**). Provocation tests with FricTest ® (Moxie, Berlin, Germany) are done by placing the four pins on the skin and then moving them horizontally across the skin test site. By stroking with these four pins, the skin is exposed to four defined trigger strengths (**c**). The test result is positive, when an itchy wheal develops at the provocation site within 10 min. In patients with severe symptomatic

double-stranded DNA (Hatada et al. 2013), or interleukin-24 (Schmetzer et al. 2018). Additional signals that are held to have important effects on mast cells in CSU include complement components such as C5a (Ferrer et al. 1999) and neuropeptides, for example substance P (Metz et al. 2014; Vena et al. 2018), some of which may act via the receptor MRGPRX2, which has been reported to be upregulated in skin mast cells of patients with CSU (Fujisawa et al. 2014) and can be induced by interleukin-33 (Wang et al. 2019).

5 Clinical Picture

5.1 Acute Spontaneous Urticaria

Acute spontaneous urticaria (AU) resolves within a few days to several weeks. The causes of AU include viral infections of the upper airways (the common cold) or gastrointestinal tract, IgE-mediated food allergy, and the intake of non-steroidal anti-inflammatory drugs such as ibuprofen, diclofenac, and acetylsalicylic acid. In many patients with AU, the cause cannot be identified. The clinical picture is variable in patients with AU, ranging from a few transient wheals to severe angioedema of several days' duration with hundreds of simultaneous and sometimes confluent wheals that affect large body areas and come with systemic impairment.

5.2 Chronic Spontaneous Urticaria

Wheals and angioedema can occur together or alone in patients with CSU. About 50% of CSU patients develop both, wheals and angioedema. About 40% and 10% of patients experience solely wheals and solely angioedema, respectively (Maurer et al. 2011a). CSU is of long duration in most patients and shows spontaneous remission in virtually all patients. About 50% of patients with CSU are affected for more than 10 years (van der Valk et al. 2002), and the average duration of CSU ranges from 4 to 7 years. In most patients with moderate or severe CSU, wheals and/or angioedema

Fig. 2 (continued) dermographism, all four pins of Frictest® induce a positive response (**d**). In patients with mild symptomatic dermographism, only the longest pin results in a positive response (**e**). In (**d**) and (**e**), numbers indicate the four pins with 1 = the longest pin and 4 = the shortest pin; +, positive response; −, negative response. A pen-shaped dermographic tester with a spring-loaded tip is also used to assess trigger thresholds in patients with symptomatic dermographism (F, HTZ Limited, Vulcan Way, New Addington, Croydon, Surrey, UK). (**g**) shows three positive skin provocation test results induced by scratching with the dermographic tester set to three different trigger strength. The TempTest® cold and heat provocation instrument (H, Courage & Khazaka, Köln, Germany). (**i**) Positive test result in a patient with cold urticaria tested with TempTest®. (**j**) The see-through assessment template is placed on the test reaction to assess the trigger threshold, i.e. the highest temperature that produces a wheal. (**k**) Temperature threshold of 27°C determined by TempTest® in a patient with cold urticaria and high disease activity

occur every day or almost every day (Weller et al. 2011). Disease activity can change markedly over time in the same patient, with periods of weeks and months in which no symptoms occur and other times in which disease activity is high. In some patients, unspecific triggers such as stress or infections can sporadically lead to the exacerbation of CSU.

5.3 Chronic Inducible Urticaria

In patients with CIndU, wheals and angioedema are induced by specific triggers, such as cold in cold urticaria and scratching in symptomatic dermographism. 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. This makes CIndU a more predictable disease than CSU in terms of its clinical picture. 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 (Maurer et al. 2011a). 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.

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. Trigger thresholds, i.e. the sensitivity to symptom-inducing triggers, are rather constant in most patients with CIndU. 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 more often than other skin sites, 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.

6 Diagnostics

6.1 Acute Spontaneous Urticaria

Patients with ASU, in most cases, do not need a diagnostic workup with the exception of taking the patient's history. The disease is self-limited, and diagnostic test, when performed, often fails to identify the cause. There is one exception to this rule: In patients where ASU is suspected to be due to an allergy, based on the patient's history, an allergy to food for example, allergy tests and patient education can help to avoid subsequent exposure to the causative allergen.

6.2 Chronic Spontaneous Urticaria

In patients with CSU, the diagnostic workup can have several aims such as the exclusion of a severe inflammatory condition and of differential diagnoses, the search for the underlying cause and relevant aggravators, the evaluation of disease activity, impact, and control, the assessment of comorbidities, and the characterization of predictors of the course of the disease or the response to treatment. Physicians should be clear, in their communication with patients, which diagnostic tests are done and why.

In all patients with CSU, the erythrocyte sedimentation rate and/or C-reactive protein should be measured, and a differential blood count should be done. This is to rule out severe inflammatory conditions including autoinflammatory differential diagnoses.

Patients with long-standing CSU and/or high disease activity may benefit from tests that are aimed at the investigation of the underlying cause or of relevant aggravators. This search should be based on clues from the patient's history, and it should focus on common causes of CSU such as autoimmunity and autoallergy as well as common aggravating conditions such as chronic infections, stress and intolerance to food components.

Autoimmunity and autoallergy are harmful responses of the body to itself, and they involve IgG autoantibodies and IgE autoantibodies, respectively (Maurer et al. 2018a). Both have been linked to CSU and are held by many to be the underlying cause in most patients with CSU. Autoimmune CSU (aiCSU) does not come with distinct clinical features, but high disease activity, angioedema, poor response to antihistamines and omalizumab therapy, and autoimmune comorbidities have been described to be more frequent in patients with aiCSU. Also, elevated levels of anti-TPO and ANA and low levels of IgE have been reported to be more common in patients with aiCSU. The tests performed for aiCSU include the autologous serum skin test, cellular activation tests such as the basophil histamine release test or the basophil activation test, and assays for IgG autoantibodies to IgE or FcϵRI. Autoallergic CSU (aaCSU) comes with IgE autoantibodies to 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). Like aiCSU, aaCSU does not come with distinct clinical features. High normal or elevated total IgE levels and a fast and good response to omalizumab treatment have been reported to be linked to aaCSU (Kolkhir et al. 2017a; Kolkhir et al. 2017b; Maurer et al. 2011b). As of now, tests to diagnose aaCSU, i.e. assays for IgE autoantibodies or total auto-IgE, are not commercially available.

Bacterial infections, for example of the gastrointestinal tract by *Helicobacter pylori* or chronic ear nose or throat infections, as well as viral infections can aggravate CSU. However, most studies indicate that eradication of *Helicobacter pylori* has no discernible effect on CSU beyond that of standard CSU therapy (Curth et al. 2015; Kim et al. 2019). Still, it may not be irrelevant, as one recent study showed that inflammation linked to *Helicobacter pylori* infection can lead to reflux and that patients who are successfully treated for reflux, but not those who are not,

can experience remission of their CSU (Zheleznov et al. 2018). Many patients with CSU suspect that their condition is due to what they eat and drink, and food intolerance, for example to preservatives or to naturally occurring aromatic compounds, has been linked to CSU in about one out of three patients (Magerl et al. 2010; Zuberbier et al. 1995). In a small study with 45 CSU patients and 45 healthy controls, stress has been described to aggravate CSU and to contribute to high levels of disease activity (Varghese et al. 2016). Assessing patients with CSU for the relevance of these known aggravators can help with the management of their disease.

The diagnostic workup, in all patients with CSU, should aim to assess and monitor 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 is based on the daily documentation, usually once daily for seven consecutive days (UAS7), of the number of wheals and the intensity of pruritus during the previous 24 h (Hawro et al. 2018; Hollis et al. 2018). It 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). The sum of the daily totals of these wheal and itch scores is the value of the UAS7, it ranges from 0 (no disease activity) to 42 (maximum disease activity). 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).

In addition to the activity of their disease, patients with CSU should be assessed for the impact of the disease on their lives including its effects on their quality of life. The CU-Q_2oL (Chronic Urticaria Quality of Life Questionnaire) and the AE-QoL (Angioedema Quality of Life Questionnaire) are disease-specific instruments to assess the impairment in quality of life in patients with CSU who have wheals and angioedema, respectively (Baiardini et al. 2005; Mlynek et al. 2009; Weller et al. 2012, 2016).

The guideline-recommended tool for assessing disease control in patients with CSU is the urticaria control test (UCT) (Weller et al. 2014). 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 diagnostic workup of patients with CSU should include their evaluation for comorbidities. Autoimmune diseases, for example, are well recognized to be more common in patients with CSU (Kolkhir et al. 2016, 2017a, b, c). There is increasing evidence that mental disorders are also more prevalent and under-recognized. Some comorbidities including mental disorders and CIndU add to the burden of CSU and to the impairment of quality of life in patients with 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, 2018a; Larenas-Linnemann et al. 2018). For all of these reasons, patients with CSU should be assessed for comorbidities.

Finally, it is useful to assess patients with CSU for predictors of the course of their disease and for their response to treatment. Higher age at onset of CSU, being female, long CSU duration and aspirin/NSAID hypersensitivity have been reported to be linked to severe CSU and a long time to spontaneous remission. In addition, comorbidity of CIndU and the occurrence of angioedema may point to longer CSU duration, whereas a positive autologous serum skin test appears to be linked to higher disease activity (Sanchez et al. 2019). Patients with CSU, who are non-responders to antihistamine treatment, have higher C-reactive protein levels as compared to responders (Kolkhir et al. 2018b). Serum autoreactivity as assessed by basophil histamine release or autologous serum skin testing and low levels of IgE and failure of IgE to increase after the start of treatment have been reported to predict poor or slow treatment responses in patients treated with omalizumab (Ertas et al. 2018; Marzano et al. 2018; Nettis et al. 2018; Weller et al. 2018a).

6.3 Inducible Urticarias

The diagnostic workup, in patients with CIndU, should exclude differential diagnoses, aim to identify and characterize the relevant elicitation trigger(s), and evaluate disease activity, impact and control (Magerl et al. 2016). A search for underlying causes is not recommended as these are currently not known.

In symptomatic dermographism, formerly also called urticaria factitia or dermographic urticaria, scratching of the skin is the relevant wheal-inducing trigger. Provocation tests 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: (1) FricTest® (Moxie, Berlin, Germany, Fig. 2) is used for simultaneous testing of four defined trigger strengths. (2) 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, UK, Fig. 2). Both of these dermographometers are used for provocation testing by placing them on the skin and then moving them vertically across the skin test site. The test result is positive, when an itchy wheal develops at the provocation site within 10 min. Positive provocation tests should be followed up by threshold testing (Magerl et al. 2016) (Fig. 2). Patients with symptomatic dermographism should be monitored for their disease activity, response to treatment, and control of the disease by threshold testing and use of the UCT at every visit.

In delayed pressure urticaria, skin exposure to vertical pressure is the relevant trigger, e.g. pressure from the shoulder straps of heavy bags, tight shoes, or prolonged sitting. Patients with delayed pressure urticaria typically develop erythematous angioedema-like swellings, not wheals, and these swellings develop hours after exposure to pressure with a delay of 4–8 h, rather than fast. Also, these swellings typically persist for several hours, in some patients for several days. Provocation and threshold testing for delayed pressure urticaria 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.

In vibratory angioedema, skin exposure to vibration is the relevant trigger, and this results in cutaneous swellings that occur within minutes after exposure at exposed skin sites. Provocation testing can be done with a laboratory vortex mixer.

In cold urticaria, skin exposure to cold is the relevant trigger. Patients with cold urticaria show itchy wheal and flare type skin reactions or angioedema at exposed skin sites, typically within minutes after cold contact (cold air, cold liquids or objects). Provocation testing 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 & Khazaka, Köln, Germany) (Magerl et al. 2015, 2016; Maurer et al. 2018a, b, c, d) (Fig. 2). Threshold measurements and use of the UCT at every visit allow patients and physicians to monitor disease activity, the therapeutic response, and disease control.

In heat urticaria, wheals develop within minutes and resolve within a few hours at skin areas exposed to heat. 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.

In solar urticaria, exposure to UV and/or visible light is the relevant trigger, and skin responses are characterized by itchy wheals that occur within minutes at exposed skin sites. 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.

In cholinergic urticaria, sweating is the relevant trigger and results in itching and whealing, typically within minutes and for less than 1 h. 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 to assess disease activity, together with the cholinergic urticaria activity score, CholUAS (Altrichter et al. 2014). Disease control and impact are assessed by use of the UCT and the cholinergic urticaria quality of life questionnaire (CholU-QoL), respectively (Ruft et al. 2018).

7 Therapy

7.1 Acute Spontaneous Urticaria

In the management of ASU, the therapeutic goal is to control and prevent the development of urticarial lesions until the condition resolves by itself. Future exposure to known and circumventable elicitors should be avoided. Patients with minimal or mild ASU may not require treatment or respond to an oral non-sedating H_1-antihistamine, which should be used until the recurrence of wheals subsides. In patients with moderate and severe ASU, the dose of the H_1-antihistamine may need to be increased up to fourfold the standard dose, and the addition of an oral steroid should be considered.

7.2 Chronic Spontaneous Urticaria

In CSU, the aim of treatment is to stop the reoccurrence of wheals and/or angioedema. In most patients, the use of prophylactic medication rather than attempts to eliminate suspected causes or aggravators is the strategy of choice.

The first-line symptomatic treatment for CSU is a second generation, non-sedating H_1-antihistamine (Zuberbier et al. 2018). The response to this treatment should be monitored by the use of the UAS and/or AAS as well as the UCT. In patients where this does not prevent the occurrence of wheals and angioedema and does not control the disease after 2–4 weeks, the dose of the non-sedating H_1-antihistamine should be increased to up to four times the standard dosage. This is more effective than standard-dosed antihistamine treatment, and it is safe and well tolerated with antihistamines that are non-sedating at higher than standard doses (Gimenez-Arnau et al. 2009; Staevska et al. 2010; Weller et al. 2018b). Patients who fail to achieve control of their CSU with a higher than standard-dosed H_1-antihistamine are treated with add-on omalizumab, best given at 300 mg every 4 weeks. The efficacy and safety of omalizumab in the treatment of patients with CSU has been demonstrated in clinical trials and real life (Gimenez-Arnau et al. 2016; Zhao et al. 2016). Multiple mechanisms have been suggested to contribute to the therapeutic effects of omalizumab in patients with CSU as well as for the heterogeneity of their clinical responses experienced by patients (Chang et al. 2015; Gericke et al. 2017; Metz et al. 2017a, 2019). Patients with complete control of their signs and symptoms should be assessed for spontaneous remission of their CSU every 6–12 months.

7.3 Chronic Inducible Urticaria

The management of CIndU aims to control the disease, completely, and to prevent the induction of wheals and angioedema for as long as it takes, i.e. until spontaneous remission occurs. To this end, patients should be advised to monitor trigger

thresholds and to document the activity, impact, and control of their CIndU, to avoid or mitigate relevant triggers, and to use prophylactic medication. All CIndU patients should know that modifying or stopping the exposure to relevant triggers can help, and they should be made familiar with strategies to do so. Patients with DPU, for example, should avoid, if possible, tight fitting shoes, if wearing them results in swelling of their feet, and give preference to soft and loose-fitting ones. Importantly, CIndU can have devastating effects on patients' quality of life when trigger thresholds are low and trigger avoidance interferes with daily routines and a normal daily life.

In patients with CIndU, a second-generation non-sedating H_1-antihistamine at standard and higher than standard dose is the first-line and the second-line treatment, respectively (Maurer et al. 2018b; Dressler et al. 2018). Higher than standard antihistamine doses are more effective than standard-dosed treatment, and they are often needed to prevent whealing and angioedema and to achieve disease control (Abajian et al. 2016; Krause et al. 2013; Magerl et al. 2012). Omalizumab, although off label, is the recommended treatment for patients with antihistamine-resistant CIndU, based on controlled trials and clinical experience (Maurer et al. 2017, 2018d; Metz et al. 2017b). In patients with CIndU who fail to respond to omalizumab treatment, other therapies that have been reported to be of benefit should be considered. Examples include cyclosporine A or antibiotic treatment with doxycycline for cold urticaria (Gorczyza et al. 2017), UVB light therapy for symptomatic dermographism (Borzova et al. 2008), the humanized interleukin-5 antagonist monoclonal antibody reslizumab (Maurer et al. 2018c) or anti-TNFα (Magerl et al. 2007) in delayed pressure urticaria, and afamelanotide, a synthetic peptide and analogue of α-melanocyte stimulating hormone, for solar urticaria (Haylett et al. 2011).

In some types of CindU such as solar urticaria, cold urticaria, and cholinergic urticaria, desensitization to the eliciting trigger is possible. But this treatment is often not tolerated well and patient compliance is poor. Patient compliance, however, is crucial for this treatment to be successful, because daily exposure of the patients to their specific trigger (e.g., daily cold showers in patients with cold urticaria) is needed to achieve and maintain the depletion of urticaria-eliciting mediators and the protection from trigger-induced wheals and angioedema.

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