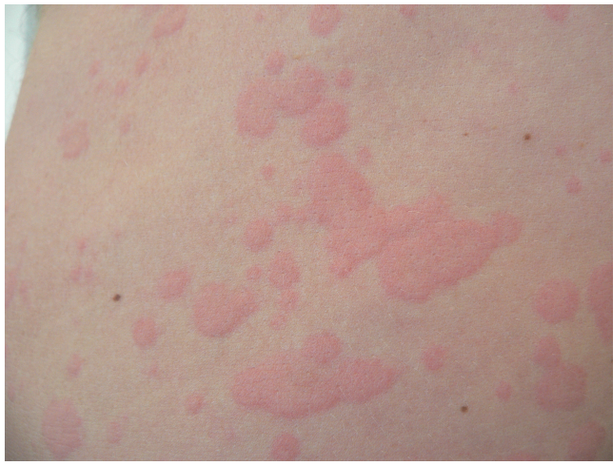
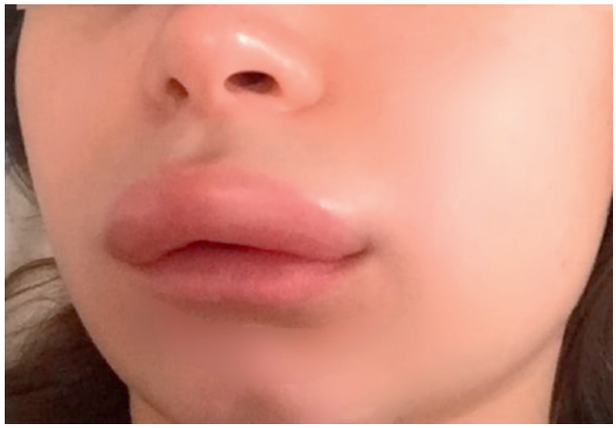
249

Urticaria and angioedema

Marcus Maurer, Torsten Zuberbier, Martin Metz





Urticaria is a frequent disease affecting up to 20% of us at least once during our lifetime. The hallmark feature of urticaria is the wheal, which is caused by mast cell–derived mediators such as histamine producing a transient increase in the permeability of cutaneous blood vessels, resulting in a short-lived superficial skin swelling. In addition to wheals (sometimes called hives), many urticaria patients also develop deep swellings of the dermis and subcutis, known as angioedema. Some urticaria patients exclusively experience angioedema, never having wheals. Wheals and angioedema as symptoms are not pathognomonic for urticaria; that is, patients with other diseases may experience whealing or angioedema. For example, angioedema without wheals can be mediated by bradykinin, independently of mast cell degranulation and histamine, and wheals also occur in patients with urticarial vasculitis or autoinflammatory syndromes, which are mediated by interleukin-1 rather than mast cell–derived histamine or bradykinin.

URTICARIA

INTRODUCTION

The signs and symptoms of urticaria are brought about by the degranulation of cutaneous mast cells. Skin mast cells are preferentially localized in the vicinity of sensory nerves and small blood vessels. Their activation by certain signals, such as immunoglobulin E (IgE) crosslinking, can lead to their degranulation and release of *de novo* synthesized and preformed mediators, e.g., histamine. These mediators induce sensory nerve stimulation (itch, burning pain), vasodilatation (flare), edema (wheal, angioedema), and the recruitment of immune cells such as eosinophils, basophils, and neutrophils.

Clinically, urticaria is characterized by the rapid development of wheals, angioedema, or both. Wheals are associated with itching or burning as well as a flare reaction. They resolve spontaneously, usually within a few hours. In contrast, angioedema is a deeper, pronounced, and sometimes painful swelling of the lower dermis and subcutis and can also affect the mucous membranes. Swellings are of longer duration and slower resolution than wheals and can last for several hours to a few days. Angioedema, in patients with urticaria, can certainly be very debilitating and frightening. Patients need to be reassured that, unlike swelling attacks in patients with hereditary angioedema, urticaria-associated angioedema is not fatal.

Urticaria is either acute (less than 6 weeks' duration) or chronic. Urticaria patients develop wheals and/or angioedema spontaneously (spontaneous urticaria) or in response to a specific trigger (inducible urticaria). The specific triggers of whealing and angioedema formation in chronic inducible urticaria can be physical, e.g., contact with cold or heat (cold urticaria, heat urticaria), irradiation with ultraviolet (UV) light or visible light (solar urticaria), friction (symptomatic dermographism), pressure (pressure urticaria), or vibration (vibratory angioedema). In contrast to these physical forms of inducible urticaria, the development of signs and symptoms in the other types of inducible urticaria is triggered by skin contact with urticariogenic substances (contact urticaria), water (aquagenic urticaria), or sweat (cholinergic urticaria).

In chronic spontaneous urticaria (CSU), both wheals and angioedema can occur anywhere on the body. However, wheals appear most often at the legs and arms and rarely in the face, whereas angioedema is most commonly localized in the face (e.g., the lips and eyes). In contrast, chronic inducible urticaria is usually characterized by whealing and/or angioedema formation at the skin sites that are exposed to the eliciting trigger. Disease activity and control in CSU urticaria is assessed using the urticaria activity score (UAS7) and the angioedema activity score (AAS), which rely on prospective patient documentation of daily wheal numbers and itch intensity (UAS7) and swellings (AAS), and the urticaria control test (UCT) and angioedema control test (AECT), respectively. The UCT and the AECT are validated and reliable 4-item retrospective tools, distinguishing patients with poorly or uncontrolled disease versus well or completely controlled disease. Disease activity in patients with inducible urticarias is measured by assessing trigger thresholds via provocation testing.

Important differential diagnoses of urticaria are severe allergic reactions (e.g., anaphylactic shock), where wheals and/or angioedema co-occur with systemic manifestations, urticarial vasculitis, autoinflammatory syndromes, and bradykinin-mediated angioedema (e.g., hereditary or acquired C1 inhibitor deficiency).

MANAGEMENT STRATEGY

The aim of the treatment of patients with urticaria is the elimination of signs and symptoms. This may be achieved by treating an underlying cause or condition, by the avoidance of eliciting triggers, by preventing mast cell degranulation, or by blocking the effects of histamine or other mast cell mediators. For the inducible urticarias, causes are largely unknown and their triggers of wheal and/or angioedema development may be difficult or impossible for patients to avoid. Urticaria is self-limiting but often lasts for several years and, in some cases, for decades. Effective and safe prophylactic therapy aimed at the prevention of signs and symptoms is, therefore, needed, and several treatment options are available. The prevention of recurring urticaria signs and symptoms by medication that protects patients from the effects of relevant mast cell degranulating signals or of the mediators released by mast cells is currently the most common approach for the management of urticaria.

Acute Urticaria

Acute urticaria in most patients can be managed with oral *second-generation H1-antihistamines* (sgAHs) (Table 249.1). Add-on oral glucocorticosteroids may be used for a few days for severe cases, and they can reduce disease activity and duration when given at the onset of the disease.

Chronic Spontaneous Urticaria

By taking a good history and asking the patient to keep a symptom diary, it is sometimes possible to identify exacerbating factors that increase disease activity, e.g., stress, infections, gastritis, or the intake of non-steroidal antiinflammatory drugs. Avoiding these triggers, where possible, can help to reduce disease activity.

Current guidelines recommend a step-up approach for the pharmacological treatment of patients with CSU, with standard-dosed (first-line therapy) and up to fourfold dosed sgAHs (second-line therapy) followed by add-on omalizumab (third-line therapy). In patients who do not respond to omalizumab, ciclosporin is recommended as fourth-line treatment. Based on the available evidence and experience, these treatment options work in most patients and should be explored before moving to other therapies.

The signs and symptoms of CSU are largely driven by mediators released from activated skin mast cells. The most prominent one is histamine, which exerts its action via H1-receptors on cutaneous blood vessels and nerves. The first-line pharmacological approach for the treatment of all patients with CSU is, therefore, the use of sgAHs at licensed doses. All sgAHs are inverse agonists that promote the inactivate state of the H1-receptor and prevent its binding of histamine. SgAHs should, therefore, be taken regularly, i.e., every day, to prevent histamine-mediated extravasation and to protect from the development of skin lesions, rather than as on-demand medication after skin lesions have already developed. SgAHs are highly selective for the H1-receptor and minimally or non-sedating because of their low penetration of the blood–brain barrier, an important difference to first-generation antihistamines. The use of standard-dosed sgAHs as first-line therapy of CSU is supported by a large body of high-quality evidence for their efficacy and safety from numerous randomized controlled trials. Current guidelines recommend against the routine use of first-generation H1-antihistamines (AHs) in the management of CSU, as they can have anticholinergic effects, cause sedation, impair the quality of sleep, affect cognitive and psychomotor functions, and exhibit interactions with other drugs.

Table 249.1 Selection of second-generation H1 antihistamines used in the treatment of chronic urticaria

Second-generation antihistamine	Daily standard dose
Bilastine	20 mg
Cetirizine	10 mg
Desloratadine	5 mg
Ebastine	10 mg
Fexofenadine	180 mg
Levocetirizine	5 mg
Loratadine	10 mg
Mizolastine	10 mg
Rupatadine	10 mg

In patients with CSU who continue to show signs and symptoms after 2–4 weeks of standard-dosed sgAH treatment (or earlier, if symptoms are intolerable) updosing of the sgAH to up to fourfold the licensed dose is suggested. This second-line therapy, with one sgAH at a higher than standard dose, is preferable to combining different H1-antihistamines at the same time in the same patient. The recommendation to updose sgAHs in treatment-resistant patients is based on several randomized controlled trials, numerous real-life surveys, and longstanding and broad experience, all of which support the notion that updosed sgAHs show higher efficacy in CSU as compared to standard dose sgAH treatment. In general, higher than standard doses of sgAHs are held to be safe and well tolerated, even with long-term use. Most modern sgAHs have been described to also have antiinflammatory effects, often only at high doses. However, individual sgAHs exhibit differences in the strength of the evidence in support of their safety and efficacy when used at higher than standard doses. Thus, responses to treatment, in terms of both disease control and sedation or other possible side effects, need to be monitored continuously.

Most patients with CSU benefit from sgAH treatment, but many do not show complete control. In patients who still have urticaria signs and symptoms after 2–4 weeks of high-dose sgAH therapy, or earlier, if symptoms are intolerable, add-on treatment with *omalizumab* should be considered. The long-term use of *systemic glucocorticosteroids* is to be avoided, but a short course may be tried to control acute exacerbation. Omalizumab is a humanized antibody against IgE licensed for the treatment of asthma and CSU. A meta-analysis of its use in seven randomized controlled trials found omalizumab to be very safe and effective in patients with CSU who were treatment-resistant to H1-antihistamine treatment in licensed doses or up to four times the licensed dose.[1] The first randomized controlled trial performed in CSU used the omalizumab dosing regimen established for severe asthma, but subsequent trials revealed that urticaria symptoms and quality of life improved significantly with a standard dose of 150 mg or 300 mg/4 weeks omalizumab, independent of body weight and IgE serum levels. The largest decrease of disease activity and the highest number of patients with complete response were found in the 300-mg group. Similar to antihistamines, omalizumab is a symptomatic rather than a curative treatment, and the adaptation of dosing and treatment intervals to fluctuations in disease activity should be considered, based on continued monitoring of disease activity, control, and impact on patients.

The treatment of patients with CSU with omalizumab during the past years confirms the good risk/benefit profile of this therapy seen in clinical trials. It also indicates that the onset of action of omalizumab in most patients is fast, often within a few days after the first administration, but that up to five treatments may be needed for some patients to respond. Most omalizumab-treated patients with CSU can stop all concomitant therapies and remain free of symptoms with omalizumab alone. Omalizumab appears to be effective in CSU patients with both wheals and angioedema, as well as those suffering from isolated angioedema.

The use of *ciclosporin* as a back-up treatment option in treatment-resistant patients is supported by the longstanding experience and evidence that this drug can be effective in patients with CSU. Ciclosporin is usually given over 3–4 months at a starting dose of 2–4 mg/kg/day with a fast onset of action, usually within a week, in most patients. When working with ciclosporin, its known side effects including hypertension, hypertrichosis, increase of creatinine levels up to renal failure, and dyslipidemia need to be considered, requiring careful monitoring.

Many other treatments have been used in CSU, but their effects have either not been studied in controlled settings or the strength of the evidence in support of their use is low. Treatments that may be used in CSU patients who are treatment-resistant to sgAHs, omalizumab, and/or ciclosporin include, but are not limited to, autologous whole blood or *serum therapy, azathioprine, benralizumab, cyclophosphamide, colchicine, dapsone, dupilumab, H2-antagonists, intravenous immunoglobulins, leukotriene antagonists, mepolizumab, methotrexate, mycophenolate mofetil, and reslizumab.*

Chronic Inducible Urticaria

The treatment approaches and medications used for chronic inducible urticarias are, by and large, very similar to those for CSU. Patients can benefit from knowing what triggers their urticaria and knowing their individual trigger threshold, as this can help them avoid situations that are associated with disease exacerbation. For many forms of chronic inducible urticaria, however, it is exceedingly difficult or impossible for patients to completely avoid any exposure to the eliciting trigger, for example, mechanical irritation of the skin in symptomatic dermographism. Because of this, pharmacological treatment is very important and needed for most patients with chronic inducible urticaria.

SgAHs are the first-line treatment of choice, and doses should be increased up to fourfold in patients who do not respond. All sgAHs are licensed for the use in chronic inducible urticarias. Moreover, based on clinical experience and some studies, they are effective and safe in all forms of chronic inducible urticaria. However, for most forms of chronic inducible urticaria, no controlled studies have been performed with standard-dosed and/or higher than standard doses of sgAHs. Several case series and reports as well as a few randomized controlled trials and meta-analyses indicate that omalizumab is effective and safe for the treatment of patients with inducible forms of chronic urticaria, but it is not licensed for this use.[2]

Other treatments for patients with chronic inducible urticaria are, in general, backed only by weak evidence or no evidence and come with concerns regarding their risk/benefit profiles. For example, in some forms of chronic inducible urticaria such as cold urticaria, solar urticaria, and cholinergic urticaria, tolerance can be induced by *desensitization* protocols using repeated exposure to the relevant trigger with gradually increasing strength. However, this tolerance is transient, patients usually require daily maintenance exposure, and severe side effects have been described.

Specific Investigations

Acute urticaria

- None

Chronic spontaneous urticaria

- Exclude differential diagnoses, screen for comorbidities (e.g., chronic inducible urticaria, other autoimmune diseases, depression/anxiety)
- Check for systemic inflammation (CRP, ESR, and/or differential blood count)
- Assess disease activity, impact, and control, e.g., by use of the urticaria activity score (UAS7)/angioedema activity score, the chronic urticaria quality of life questionnaire (CU-Q2oL)/angioedema quality of life questionnaire (AE-QoL), and the UCT/AECT, respectively
- In patients with uncontrolled or longstanding disease, consider underlying causes based on history and physical examination (e.g., total IgE measurements, autologous serum skin testing, basophil activation assay [when available in cases of suspected autoimmunity])

Chronic inducible urticaria

- Exclude differential diagnoses
- Confirm relevance of trigger(s) by provocation testing
- Determine disease activity and control by assessing trigger threshold and use of the UCT, respectively

First-Line Therapy

- Second-generation H1 antihistamines **A**

Second-Line Therapy

- Up to fourfold standard dose second-generation H1 antihistamines **A**

Third-Line Therapy

- Omalizumab **A**

Fourth-Line Therapy

- Ciclosporin[3] **A**

The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Zuberbier T, Aberer W, Asero R, et al. Allergy 2018; 73(7): 1393–414.

The definition, diagnostic testing, and management of chronic inducible urticarias – the EAACI/GA(2) LEN/EDF/UNEV consensus recommendations 2016 update and revision. Magerl M, Altrichter S, Borzova E, et al. Allergy 2016; 71(6): 780–802.

NON-MAST CELL–MEDIATED ANGIOEDEMA

INTRODUCTION

In contrast to mast cell–mediated angioedema, which is a frequent feature and sign of chronic urticaria, non-mast cell–mediated angioedema is a group of diseases. These include hereditary angioedema (HAE) (see Ch. 101) with or without C1 inhibitor (C1INH) deficiency, angioedema due to acquired C1INH deficiency, and drug-induced angioedema, such as angiotensin-converting enzyme inhibitor-associated angioedema. Patients with these angioedema diseases, all of which are held to be bradykinin-mediated, usually do not exhibit wheals.

Two major forms of HAE, both rare, have been described: HAE with C1INH deficiency, subclassified as type I and type II based on low antigenic and functional C1INH levels, respectively, and HAE with normal C1INH levels with or without known mutations, e.g., in Hageman factor (coagulation factor XII). Angioedema attacks in all type I and type II HAE patients are held to be due to the enhanced generation of bradykinin. The acquired forms of non-mast cell mediator–mediated angioedema include those that are due to acquired C1INH deficiency (e.g., increased catabolism of C1INH) and those that are due to certain drugs, mainly angiotensin-converting enzyme inhibitors (ACEI). Like in HAE, attacks of patients with these forms of angioedema are linked to bradykinin.

In patients with HAE due to C1INH deficiency, recurrent angioedema attacks primarily involve the hands and feet, the abdomen, the face, the oropharynx, or a combination of the above. Patients with HAE due to C1INH deficiency often experience prodromal symptoms (e.g., erythema marginatum). Typical attacks progress for several hours and then slowly resolve over many hours to several days. Attacks involving the extremities and abdomen are the most common, and attacks of the oropharynx are the most dangerous, with a significant risk of mortality due to suffocation. In comparison, HAE with normal C1INH is more likely to affect females, to first occur after puberty, and to come with fewer attacks. Triggers of attacks are common and similar in all forms of HAE and include trauma, increased estrogen levels, and stress.

Attacks in patients with angioedema due to acquired C1INH deficiency are similar to those of HAE patients, but the former show a later age of onset and no family history. Attacks in patients with ACEI-induced angioedema typically affect the face, especially the lips and tongue. The time to onset of angioedema attacks after the start of ACEI treatment is usually less than 1 month, but in one of four affected patients it is greater than 6 months, and up to 10 years in some patients.

The diagnosis of bradykinin-mediated angioedema requires a thorough history, exclusion of differential diagnoses (especially chronic urticaria), and laboratory testing for C1INH deficiency. Angioedema in patients taking an ACEI is due to the ACEI until or unless proven otherwise.

MANAGEMENT STRATEGY FOR BRADYKININ-MEDIATED ANGIOEDEMA

The management of HAE with C1INH deficiency consists of the avoidance of known triggers of attacks and pharmacotherapy, i.e., the use of on-demand treatment for attacks, their prevention by prophylactic treatment, or both. Today, five highly effective and safe drugs are available for the on-demand treatment of attacks, three different *C1 inhibitors* (C1INHs, two plasma-derived and one recombinant) as well as *icatibant*, a selective bradykinin B2 receptor antagonist, and *ecallantide*, which inhibits plasma kallikrein, the protease that cleaves kininogen and generates bradykinin. Patients with HAE due to C1INH deficiency may also require prophylaxis. Preprocedural prophylaxis is usually done with C1INH with the aim to protect patients from attacks that occur in response to unavoidable triggers such as dental work or surgery. Long-term prophylaxis, i.e., the regular use of medication to prevent angioedema attacks, should be considered in all HAE patients with C1INH deficiency, especially in those with high attack frequency and severity or limited access or response to on-demand treatment. *Lanadelumab*, the oral kallikrein inhibitor *berotralstat*, a therapeutic antibody that inhibits plasma kallikrein, and C1INH are the preferred treatments for long-term prophylaxis. Patients with HAE and normal C1INH as well as patients with acquired bradykinin-mediated angioedema can also benefit from on-demand treatment with C1INH or icatibant. Importantly, the standard treatment for attacks in patients with mast cell mediator–mediated angioedema, such as glucocorticosteroids or H1-antihistamines, do not have any beneficial effect on HAE attacks and should not be used as on-demand medication for the treatment of bradykinin-mediated angioedema attacks.

Specific Investigation

- C4, C1INH level and function

Guideline for the management of hereditary angioedema: World Allergy Organization consensus document.[4]

First-Line Therapies

On-Demand

• C1INH	A
• Ecallantide	A
• Icatibant	A

Prophylaxis

• C1INH	A
• Lanadelumab	A
• Berotralstat	A

An evidence based therapeutic approach to hereditary and acquired angioedema. Bork K. Curr Opin Allergy Clin Immunol 2014; 14(4): 354–62.

Lanadelumab for the prevention of attacks in hereditary angioedema. Valerieva A, Senter R, Wu MA, et al. Expert Rev Clin Immunol 2019; 15(12): 1239–48.

Lanadelumab, a human monoclonal antibody targeted against plasma kallikrein has been approved for prevention of symptoms in C1-INH-HAE.

References

1. Zhao ZT, et al. Omalizumab for the treatment of chronic spontaneous urticaria: a meta-analysis of randomized clinical trials. *J Allergy Clin Immunol*. 2016;137(6):1742–17450. e4.
2. Maurer M, et al. Omalizumab treatment in patients with chronic inducible urticaria: a systematic review of published evidence. *J Allergy Clin Immunol*. 2018;141(2):638–649.
3. Vena GA, Cassano N, Colombo D, et al. Cyclosporine in chronic idiopathic urticaria: a double blind, randomized, placebo-controlled trial. *J Am Acad Dermatol* 2006;55(4):705–709.
4. Maurer M, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. *Allergy*. 2018;73(8):1575–1596.