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## Urticaria and Angioedema Treatment

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### Abstract

Chronic urticaria (CU), one of the most frequent skin disorders, is defined as the repeated occurrence of red, swollen, itchy and sometimes painful hives (wheals), and/or angioedema (swellings in the deeper layers of the skin), for more than 6 weeks [1, 2]. CU has an estimated worldwide prevalence of approximately 1% [3], which includes spontaneous and inducible types. In chronic spontaneous urticaria (CSU), the most common type of CU, symptoms occur without a specific trigger [1, 3]. In contrast, in chronic inducible urticaria (CIndU), symptoms occur in response to specific stimuli, such as exposure to cold, heat or pressure [4]. Patients may suffer from CSU and CIndU in parallel [2]. Chronic urticaria (CU) is defined as the repeated occurrence of red, swollen, itchy and sometimes painful wheals, and/or angioedema, for more than 6 weeks. CU includes spontaneous and inducible types. In chronic spontaneous urticaria (CSU), the most common type of CU, symptoms occur without a specific trigger. Treatment of urticaria and/or angioedema mainly consist of antihistamines, short courses of corticosteroids, other immunosuppressive, and anti-inflammatory agents. Angioedema is a deeper expression of urticaria which is classified by allergic, hereditary, acquired, and angiotensin-converting enzyme inhibitor (ACEI)-induced forms.

**Keywords:** urticaria, treatment, management, angioedema

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### 1. Introduction

H1 antihistamines are usually effective in the majority of urticaria and/or angioedema patients but might be insufficient in some patients. Second-generation antihistamines are safe and effective in patients with urticaria and are the first-line agents in all guidelines. For patients not responding to monotherapy with a second-generation antihistamine in the second step, several treatments can be used including higher doses of second-generation antihistamines,

addition of H2 antagonist, or leukotriene receptor antagonists. First-generation antihistamines like hydroxyzine or doxepin can be considered in patients whose symptoms remain uncontrolled in bed time. Systemic corticosteroids are frequently used for refractory patients with urticaria and might be considered in some patients for only short-time use. Alternative therapies including omalizumab are approved by the Food and Drug Administration (FDA) for patients with chronic refractory urticaria and cyclosporine. Anti-inflammatory agents including dapsone, sulfasalazine, hydroxychloroquine, and colchicine have been used in some patients with limited evidence for efficacy in chronic urticaria.

Acute attacks of HAE are unresponsive to antihistamines or corticosteroids. C1-INH replacement, plasma kallikrein inhibitor, bradykinin receptor antagonist, and fresh frozen plasma have been approved for the treatment of acute attacks. Angioedema caused by ACE inhibitors can be an acute emergency with laryngeal or tongue edema. There is no response to antihistamines or corticosteroids. Fresh frozen plasma, C1 inhibitor, and bradykinin receptor antagonist appear to be safe and effective therapeutic options for the management of ACEI-induced angioedema.

## 2. Management of urticaria

Urticaria is commonly defined as the sudden appearance of wheals that are typically pruritic and resolve within 24 h without any skin changes, although some lesions may last up to 48 h [1]. The updated classification of urticaria distinguishes acute and chronic urticaria. Acute urticaria is defined as the one persisting less than 6 weeks, whereas chronic urticaria (CU) persists for at least 6 weeks [1]. Chronic urticaria is spontaneous (CSU) or inducible (CIU) [2]. CSU is a common disorder with a prevalence of 1% that is characterized by recurrent wheals, angioedema, or both for more than 6 weeks (with or without free intervals). CSU is self-limited but in many patients, symptoms recur for several years and can be refractory to standard therapies [3, 4].

The international urticaria guidelines advise standard dose, second-generation H1-antihistamines as first-line therapy [5]. However, H1 antihistamine treatment leads to absence of symptoms in fewer than 50% of patients, and in about 10% of cases, they fail to control the disease even at higher than licensed doses [5, 3]. Up-dosing of second-generation H1 antihistamines (up to fourfold), as recommended by the urticaria guideline as second-line therapy, can improve response, but many patients remain symptomatic. The urticaria guideline recommends add-on omalizumab, cyclosporin A (CsA) or montelukast third line in patients with an inadequate response to high-dose H1 antihistamines [5]. In refractory patients, short courses of oral steroids may induce a remission in about 50% of cases [3]. Other approaches include intravenous immunoglobulin, rituximab, dapsone, and anticoagulants are also limited by paucity of data on their efficacy and adverse effect profile [3, 6].

According to guidelines prepared in accordance with data obtained mostly in adult studies, the primarily preferred drug in acute and chronic urticaria exacerbations in children is second-generation H1 antihistamines. Guidelines recommend that the dose should be increased three

or fourfold in cases where response to H1 antihistamines treatment is not obtained at normal doses. If success of therapy cannot be achieved with H1 antihistamines used at the usual dose, high-dose H1 antihistamines is recommended. It has been reported that corticosteroids may be used short term (up to 10 days) in periods of urticaria exacerbations. However, guidelines also state that a definite recommendation cannot be made because there are insufficient randomized controlled studies in this area. The primary treatment option in long-term treatment of chronic urticaria is again second-generation nonsedative H1 antihistamines. However, the number of randomized controlled studies is substantially low for evidence-based recommendations in children. In patients who do not respond to high-dose H1 antihistaminic treatment, corticosteroid, omalizumab, cyclosporin A, and montelukast constitute tertiary treatment options. However, these drugs are recommended only in eligible patients because of the adverse effects and costs of these drugs [7].

It is clear that the current evidence-based treatment algorithm does not fit every urticaria patient. It is important that physicians do not just consult the algorithm but read the guideline line by line and employ an individualized approach for the care of each patient.

### **2.1. H1 antihistamines**

Current international guidelines recommend a licensed dose of second- or third-generation (non-sedating) antihistamines for the treatment of all forms of urticaria as the first-line therapeutic option. Second-generation H1 antihistamines include fexofenadine, loratadine, and cetirizine. Third-generation antihistamines include desloratadine and levocetirizine. These medications should be taken continuously at the lowest necessary dose rather than on demand. This treatment with licensed doses of H1 antihistamines leads to an absence of symptoms in fewer than 50% of patients with CSU [5].

If CSU symptoms persist after 2 weeks of treatment with licensed doses of second-generation H1 antihistamines, it is recommended to increase the dose up to four times the licensed dose instead of combining different H1 antihistamines to obtain control as a second-line treatment. But there are only few controlled studies that have assessed the efficacy and safety of non-sedating antihistamines [5, 6]. This dose increase results in a higher degree of efficacy in some, but not all, patients, with up to one-third of patients remaining symptomatic [5].

First-generation H1 antihistamines (diphenhydramine and hydroxyzine) are lipophilic compounds which cross the blood-brain barrier and therefore sedating and anticholinergic side effects. They impair cognitive function, learning, and performance. First-generation H1 antihistamines have been advocated for use by the US guidelines as step two therapy at night and can be titrated up to higher doses as step three therapy if tolerated by the patient. Non-sedating second- and third-generation H1 antihistamines have lower propensity to cross the blood-brain barrier. Because of this, non-sedating H1 antihistamines are favored [6].

In studies mentioned above, higher-than-standard doses of antihistamines were not associated with an increase in adverse effects in most cases. Antihistamines also have anti-inflammatory effects in the treatment of urticaria when used at higher doses than licensed

doses. Anti-inflammatory activity may result from the activation of genes responsible for the synthesis and/or synthesis of pro-inflammatory mediators [6].

## 2.2. H2 antihistamines

H2 antihistamines such as cimetidine and ranitidine are more typically used as add-on therapy in combination with H1 antihistamines and leukotriene receptor antagonists (LTRAs). A review of the Global Urticaria Forum's attendees' opinions suggested that although these agents are old and generally well tolerated by patients, they are unlikely to be used in clinical practice [8].

## 2.3. Leukotriene receptor antagonists

Cysteinyl leukotrienes are potent pro-inflammatory mediators, the effects of which can be blocked by LTRAs such as montelukast, zafirlukast, and pranlukast. LTRAs are recommended as add-on step two therapies by the US guidelines and in the third step in the Europe Union's (EU) guidelines. LTRAs have been found to significantly improve CU symptoms when used in conjunction with H1 antihistamines but are not as effective as H1 antihistamines when used as monotherapy. Combination therapy of antihistamines plus LTRAs may be more effective in patients with aspirin and nonsteroidal anti-inflammatory drug-exacerbated CSU. LTRAs appear to be well tolerated, with a good side-effect profile. Montelukast is not currently licensed for the treatment of CSU [1, 5, 9, 10].

## 2.4. Third-line treatments

If a patient's CSU symptoms persist after 1–4 weeks of second-line treatment, add-on omalizumab, CsA, or montelukast are recommended as third-line options. Both omalizumab and CsA are effective third-line CSU treatments; montelukast appears to have lower efficacy in this setting.

## 2.5. Omalizumab

Omalizumab, a humanized recombinant immunoglobulin (Ig) G1 kappa monoclonal anti-IgE, is effective in antihistamine-unresponsive patients although optimal treatment duration needs to be defined [3]. Omalizumab is currently the only agent licensed for the third-line treatment of CSU [8]. The FDA approved the omalizumab for CU is 150 to 300 mg subcutaneously every 4 weeks. The clinical response starts after 1 week at the earliest, and the complete response can be prolonged up to 4–6 months. Studies found that complete control in approximately one-third of patients, partial control in another one-third, and one-third were unresponsive [1].

Omalizumab carries a label warning for anaphylaxis, although no cases of anaphylaxis were reported in the phase III trials of omalizumab in CSU. Other known risks associated with omalizumab include increased risks of cardiac and neurovascular events and a controversial increased risk of lymphoma. Omalizumab is generally well tolerated in patients with CSU and is rated as pregnancy category B [5, 1].

## 2.6. Cyclosporin A

Cyclosporin A (CsA) could be a suitable drug for the treatment of CSU as it directly inhibits mast cell degranulation as well as targeting T-cells. Similarly, CsA directly inhibits part of the basophil histamine release assay (BHRA) [5]. Response of autoreactive CSU to CsA has been associated with disappearance of autoantibodies and CsA may be disease-modifying in these patients [5]. A low-dose CsA treatment (3 mg/kg per day or less) has been shown to cause full remission of symptoms in a number of different randomized controlled trials and real-world studies [11–14].

CsA is also effective in the majority of antihistamine-resistant CSU patients, but its use is limited by potential side effects [3]. The most common adverse events associated with the use of CsA include hypertension, fatigue, gastrointestinal problems, and headache [15]. It is also thought that long-term use of CsA may be responsible for the development of non-melanoma skin cancer [16]. In patients receiving CsA therapy, monitoring of blood pressure and renal function is particularly important [13]. CsA is not currently licensed for the treatment of CSU and should be preferred only as a short-term treatment option [5].

Cyclosporin has been reported to be effective in some studies of CSU, including three double-blind [12–18], and one study reported that 40% of patients achieved complete remission in 9 months [18].

## 2.7. Other treatment options

Other possible options for the treatment of CSU are anti-inflammatory medications (hydroxychloroquine, dapsons, sulfasalazine, and colchicine) and immunosuppressants (mycophenolate, tacrolimus, azathioprine, and methotrexate) supported by low levels of evidence as defined by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (**Table 1**).

Drug	Quality of evidence	Strength of recommendation
H2 antihistamines	Moderate	Weak (+)
Oral corticosteroids (short course)	Low	Weak (+)
Oral corticosteroids	Very low	Strong (-)
Anti-inflammatory agents (dapsons, sulfasalazine, hydroxychloroquine, colchines, mycophenolate mofetil)	Low-very low	Weak (+)
Immunosuppressive agents	Very low	Weak (+)
Methotrexate		
Cyclophosphamide		
Intravenous Ig	Low	Weak (+)

(+) recommendation for medication, (-) recommendation against medication, and Ig: immunoglobulin

**Table 1.** Quality of evidence and strength of recommendation for use of intervention in CSU based on the GRADE system.

## 2.8. Dapsone

In the current international urticaria guideline, the use of dapsone and its effectivity is still unclear. However, in a double-blind, placebo-controlled study, dapsone has been reported as a promising agent in patients with CSU unresponsive to antihistamines [19]. Supportive evidence is needed to recommend the use of dapsone in urticaria patients [8].

## 2.9. Azathioprine

Additional new therapies such as azathioprine are under investigation for use in urticaria, although the evidence supporting their use is currently limited and not robust enough to warrant a change in current guidance [8].

## 2.10. Corticosteroids

Oral corticosteroids are commonly used in management of acute urticaria, and prednisone has been shown to significantly improve control of symptoms compared to antihistamines alone. Short courses (10 days–3 weeks) of corticosteroids may be used at any time if disease exacerbations are required in CU [5, 1].

## 3. Management of angioedema

Although both urticaria and allergic angioedema are associated with mast cell activation, there are many differences between them. While urticaria affects the skin, angioedema usually affects the mucosal tissue as well. In addition, middle and papillary dermis are involved in urticaria, whereas reticular dermis and submucosal tissues are involved in angioedema. Angioedema usually resolves in less than 24–48 h, disappear without aftereffects and are more painful than itchy [20, 2, 1].

Most cases of angioedema are attributable to the histamine and bradykinin. Histamine-mediated (allergic) angioedema occurs through a type I hypersensitivity reaction, whereas bradykinin-mediated (non-allergic) angioedema is iatrogenic or hereditary in origin. Bradykinin-mediated angioedema is divided into three distinct types: hereditary angioedema (HAE), angiotensin-converting enzyme inhibitor (ACEI)-induced angioedema, and acquired angioedema (AAE) [20] (**Table 2**). Although their clinical presentations bear similarities, the treatment algorithm differs significantly from each other. Corticosteroids and epinephrine are effective only in the management of histamine-mediated angioedema [20].

Priority of the treatment of angioedema is to provide airway protection. Intramuscular epinephrine may be required in the presence of acute laryngeal edema or anaphylaxis. It is administered in adult patients at doses of 1:1000 mg 0.2–0.5 mg and in children at doses of 0.01 mg/kg (up to 0.03 mg). These doses may be repeated at intervals of 5–15 min and if necessary with monitoring [20].

Angioedema type	Clinical and diagnostic features
<b>Histamine mediated</b>	
Allergic angioedema	Angioedema is usually accompanied by urticaria and sometimes anaphylaxis, may be pruritic, and is associated with exposure to allergens; attacks last for 24–48 h; it is responsive to antihistamines and corticosteroids
Angioedema with urticarial vasculitis	Angioedema may accompanied by urticaria; there may be petechiae or purpura after swelling resolves; symptoms of underlying vasculitis
<b>Bradykinin mediated</b>	
Hereditary angioedema types I and II	Recurrent attacks without urticaria; erythema marginatum is a cardinal finding; onset of the disease in childhood or young adulthood, worsens at puberty; family history in 75% of patients; attacks unresponsive to antihistamines or corticosteroids
Hereditary angioedema type III	Associated with mutations in factor XII, more common in women, may be estrogen dependent, typical onset after childhood, face and tongue extremity involvement is more frequent than abdominal, recurrent tongue swelling is a cardinal symptom, more disease-free intervals than in HAE types I and II, family history of angioedema, and attacks are unresponsive to antihistamines or corticosteroids
Acquired angioedema	Attacks are similar to HEA, onset in middle age or later, no family history, attacks unresponsive to antihistamines or corticosteroids
ACE inhibitor-induced angioedema	History of ACE inhibitor use, no urticaria, face and tongue are the most frequent sites, more common in blacks and smokers, patients usually can tolerate ARBs
<b>Not mediated by histamine or bradykinin</b>	
Idiopathic angioedema	Angioedema sometimes accompanied by urticaria, swelling may persist for up to 48 h, attacks may occur daily, patients are responsive to antihistamines or corticosteroids
Pseudoallergic angioedema	Urticaria is typically present, usually a class-specific reaction thought to be mediated by cysteinyl-leukotriens and includes NSAID-induced angioedema, which occurs because of cyclooxygenase inhibition and subsequent release of cysteinyl-leukotriens

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAID, nonsteroidal anti-inflammatory drug.

**Table 2.** Clinical and diagnostic features of various types of angioedema.

### 3.1. Hereditary angioedema

Hereditary angioedema (HEA) is a rare, autosomal dominant disorder characterized by a quantitative (type I) or qualitative (type II) deficiency of C1 esterase inhibitor (C1-INH) protein. HAE with normal C1-INH (type III) occurs because of one of two known mutations in the gene for factor XII [20].

### 3.2. C1-INH replacement therapy

C1-INH replacement therapy maintains a central role for the treatment of angioedema attacks in patients with HAE. Berinert is a purified, pasteurized, and lyophilized form of C1-INH

concentrate which is derived from human plasma. It was approved by the US FDA in 2009 for the treatment of acute abdominal, facial, and, more recently, laryngeal attacks of HAE in adult and adolescent patients [20]. It is approved in the European Union and the USA for adults and adolescents ( $\geq 13$  years of age) for the treatment of acute angioedema attacks in patients with HEA due to C1-INH deficiency [21] (**Table 3**).

### 3.3. Plasma kallikrein inhibitor

Ecallantide (Kalbitor) received FDA approval in 2009 for use in the treatment of acute exacerbations of HEA in people aged 16 years and more. However, the EU rendered a negative opinion regarding its approval. Ecallantide can be used against attacks of HAE at any anatomical location, including abdominal/gastrointestinal, laryngeal, and peripheral attacks [22] (**Table 3**).

### 3.4. Bradykinin receptor antagonist

Icatibant (Firazyr) is a highly selective competitive bradykinin  $\beta 2$  receptor antagonist, and it is available as 30 mg in 3-ml solution as a ready-to-use syringe for immediate subcutaneous injection in an HAE attack [20] (**Table 3**).

Therapy and indication	Dosage	Monitoring tests
C1 esterase inhibitor [human] (Berinert; CSL Behring)	20U/kg body weight IV at a rate of 4 ml/min	Monitor patients with known risk factors for thrombotic events
Indicated for the treatment of acute abdominal or facial attacks of HEA in adult and adolescent patients		Epinephrine should be immediately available to treat any acute severe hypersensitivity reactions following discontinuation of administration
Plasma kallikrein inhibitor (kalbitor [ecallantide]; Dyax Corb)	30 mg (3 ml) SC in three 10-mg (1 ml) injections	Given the similarity in hypersensitivity symptoms and acute HAE symptoms, monitor patients closely for hypersensitivity reactions
Indicated for attacks at all anatomic sites	If attack persists, additional dose of 30 mg (3 ml) may be administered within a 24-h period	Administer in a setting equipped to manage anaphylaxis and HEA
Fresh frozen plasma	2U at 1–12 h before the event (only for use when C1-INH concentrate is not available)	Baseline, liver function test, hepatitis virology
Bradykinin $\beta 2$ receptor antagonist (Fizary [Icatibant] Shire Orphan Therapies)	30 mg (3 ml) injected SC in the abdominal area.	For patients who never received Firazyr previously, the first treatment should be given in a medical institution or under the guidance of a physician
Indicated for attacks at all anatomic sites	If attack persists, additional injections of 30 mg (3 ml) may be administered at intervals of $\geq 6$ h	
	No more than 3 injections in 24 h	

C1-INH, C1 esterase inhibitor; IV, intravenously; SC, subcutaneously.

**Table 3.** Treatment options of hereditary angioedema.

### 3.5. ACE inhibitor-induced angioedema

ACEI-induced angioedema is due to excessive accumulation of bradykinin. ACEI-induced angioedema is most commonly present with swelling of face, lips, tongue, and larynx and rarely involves visceral organs. Urticaria and itching are notably absent. Life-threatening edema of the upper airway is present in 25–39% of cases of ACEI-induced angioedema. Although ACEI-induced angioedema most commonly occurs shortly after treatment is initiated, it can develop long after treatment has started [20]. The nonallergic nature of the reaction renders traditional therapies (corticosteroids and antihistamines) as ineffective. Fresh frozen plasma, C1 inhibitor, and icatibant appear to be safe and effective therapeutic options for the management of ACEI-induced angioedema [22].

## 4. Management of anaphylaxis

Anaphylactic findings may include diffuse urticarial plaques, angioedema, gastrointestinal symptoms, and hypotension. In severe forms of anaphylaxis, loss of consciousness due to vascular collapse may develop. Pulmonary symptoms such as hyperinflation, peribronchial obstruction, and submucosal edema are frequently observed during anaphylaxis [20].

Elevation of lower extremities and placing in a supine position of the patient (semi-reclining if dyspneic or vomiting) are recommended [23]. An important component of acute management of anaphylaxis is volume expansion. The largest catheter possible should be placed on the largest peripheral vessel, and the rate should be titrated according to pulse and blood pressure. Adults are infused with 1–2 L iv of normal saline (5–10 mL/kg in the first 5 min) and 30 mL/kg iv in the first h in children. Antihistamines act slower than epinephrine and should not be administered alone in the treatment of anaphylaxis or acute allergic angioedema. The combined use of H1 and H2 blockers is more effective than the H1 antihistamines alone. Diphenhydramine should be administered to 25–50 mg iv in adults and 1 mg/kg iv (up to 50 mg) in children. Similar oral doses may be sufficient for mild episodes. Ranitidine should be infused 1 mg/kg iv in adults, 12.5–50 mg, iv for 10 min, in children. Inhaled  $\beta_2$  agonists are useful when bronchospasm is resistant to epinephrine injection alone. Systemic corticosteroids are not sufficient to prevent anaphylaxis. Although the use of parenteral corticosteroids (iv methylprednisolone) provides a benefit in histamine-mediated angioedema, the therapeutic effect is not immediate [20]. Epinephrine is the first choice as recommended in all guidelines. It is recommended to inject from an autoinjector IM in the mid-outer of the thigh. The first-aid dose of epinephrine is 0.01 mg/kg of a 1 mg/mL (1:1000) dilution to a maximum dose of 0.5 mg in an adult or 0.3 mg in a child. This dose can be repeated every 5–15 min as needed [24]. Intravenous epinephrine (0.1 mg in 100 mL saline, 1:100,000 solution, initially at a rate of 30–100 mL/h) may be administered in cases that do not respond to recurrent epinephrine injection and fluid therapy. Hemodynamic monitoring is recommended during intravenous epinephrine therapy [23].

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