

Histaminergic Angioedema



Paula J. Busse, MD*, Tukisa Smith, MD

KEYWORDS

- Angioedema • Histamine • Urticaria • Histaminergic • Inducible urticaria
- Spontaneous urticaria

KEY POINTS

- Angioedema, which involves the development of nonpitting edema affecting deep cutaneous layers and mucosal tissues, can be histamine or bradykinin mediated. Determining the subtype of angioedema is critical for the choice of therapy.
- Histamine-mediated angioedema is clinically distinguished by symptoms' duration (acute and chronic), the presence or absence of urticaria, and whether there are known factors inducing symptoms or not.
- Histaminergic angioedema is secondary to mast-cell and basophil activation, and therefore, the mainstay of treatment includes antihistamines, corticosteroids, and epinephrine (for emergency use).

INTRODUCTION

Angioedema is a result of increased vascular permeability with subsequent extravasation of intravascular fluid into the surrounding tissues, which include the skin, gastrointestinal (GI) tract, and upper airways.¹ Angioedema can be broadly classified into 3 categories based on the underlying mechanism and mediator producing symptoms:

1. Histaminergic angioedema
2. Bradykinin-mediated angioedema (eg, hereditary angioedema [HAE], ACE inhibitor–induced angioedema, and acquired C1 inhibitor deficiency, discussed in other articles in this issue)
3. Causes of unknown mechanisms.

There are certain key features of symptom onset and presentation that help evaluate whether angioedema is histamine or bradykinin mediated (**Table 1**). Determining

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Division of Allergy and Clinical Immunology, Icahn School of Medicine at Mount Sinai, 1425 Madison Avenue, New York, NY 10029-6574, USA

* Corresponding author.

E-mail address: paula.busse@mssm.edu

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Table 1 Differential features of histamine- versus bradykinin-mediated angioedema		
Features	Histamine Mediated	Bradykinin Mediated
Rash	Urticaria	No urticaria, occasional erythema marginatum
Family history	Atopy	Recurrent angioedema in 75% of patients with HAE
Onset/duration of symptoms	Rapid; 24–48 h	Typically slower; 3–5 d
Pruritus	Present	None, may be painful
Response to antihistamines/CS/Epi	+	–

Abbreviations: CS, corticosteroids; Epi, epinephrine.

the category of angioedema is critical for its treatment. For example, histaminergic angioedema responds to antihistamines, corticosteroids, or epinephrine, whereas bradykinin-mediated angioedema requires medications targeting this peptide and/or its pathway. Histaminergic angioedema is the most common form of angioedema and is subdivided into acute and chronic forms based on its duration of symptoms (acute <6 weeks; chronic >6 weeks) (Fig. 1). Histaminergic angioedema is further classified as that occurring with or without urticaria (wheals). The organization of histaminergic angioedema in this review is derived from several sources: the 2014 Hereditary Angioedema International Working (HAWK) Group consensus report on angioedema,² the European Academy of Allergy and Clinical Immunology (EAACI), Global Allergy and Asthma European Network (GA²LEN), European Dermatology Forum (EDF), World Allergy Organization (WAO) urticaria guideline (EAACI/GA²LEN/EDF/WAO),³ and the American Academy of Allergy, Asthma, and Immunology/American College of Allergy, Asthma, and Immunology Joint Task Force (JTF) guideline.⁴ This article reviews the

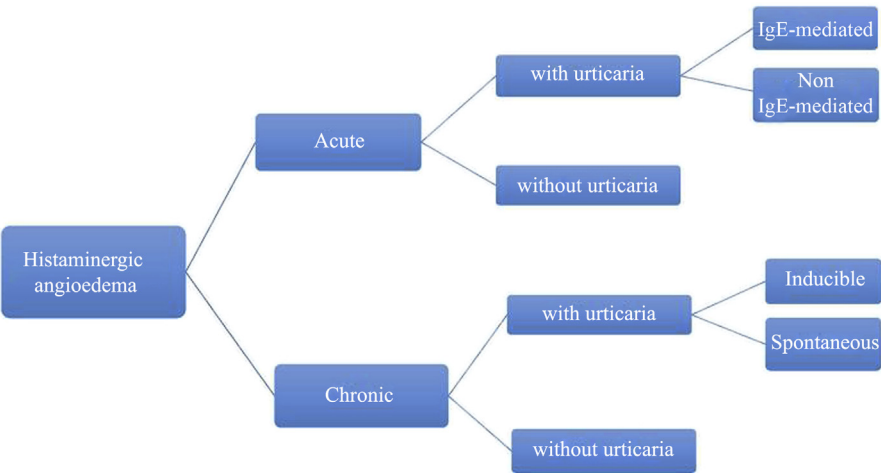


Fig. 1. Schematic of histaminergic angioedema.

subtypes of histaminergic angioedema, its presentation, pathophysiology, evaluation, and management.

ACUTE ANGIOEDEMA

Allergic (Immunoglobulin E-Mediated) Angioedema

Presentation

Allergic angioedema is frequently accompanied by urticaria; isolated angioedema as a result of an allergic response is relatively uncommon. As a mast-cell-mediated process with release of mediators, including histamine, leukotrienes, heparin, platelet-activating factor, and cytokines, there are often other symptoms, including flushing, generalized pruritus, and bronchospasm. GI pain and vomiting may be present when allergens are ingested. Often, allergic urticaria is self-limited, with symptoms resolving within 24 hours. Allergic angioedema may persist beyond this time period, but unlike bradykinin-mediated angioedema that can last 3 to 5 days, the former does not typically last longer than 24 to 48 hours. Symptoms will reoccur upon repeated exposure to the allergen or to cross-reacting allergens.⁵ The allergic reaction can progress to anaphylaxis (defined by specific criteria^{6,7}), which may result in death without appropriate treatment. Urticaria is characterized by an erythematous raised rash with an initial pale center (wheal) with intense itching. Urticarial wheals that do not have a “fleeting” nature (ie, the site of the hive on the skin does not return to its normal appearance <24 hours), those that are nonblanching, or those that leave pigment changes should prompt suspicion of an alternative diagnosis. Angioedema does not characteristically itch and is more likely to be painful. Patients typically experience angioedema and urticarial symptoms within 30 to 60 minutes after allergen exposure. Specific foods (eg, peanuts, tree nuts, shellfish, fish in adults, and milk, egg, soy in children), insect venom, medications (eg, penicillins), and environmental allergens, are common triggers producing immediate symptoms. However, some patients may develop a delayed allergic reaction, occurring 2 to 6 hours after ingestion of certain meats (eg, lamb, beef, pork) if they have developed a hypersensitivity to the carbohydrate galactose-alpha 1,3-galactose.⁸

Pathophysiology

Allergic angioedema is secondary to production of antigen (Ag)-specific immunoglobulin E (IgE) molecules in predisposed individuals following an initial exposure to this Ag. After secretion by B-lymphocytes, most Ag-specific IgE bind to their high-affinity FcεR1 receptors on the surface of mast cells and basophils, whereas the remainder circulates in the serum. When the patient is reexposed to the Ag, bound IgE molecules recognize specific proteins on the Ag, binding them, and bringing the IgE molecules closer together on the cell surface, a term called “cross-linking.” Cross-linking activates intracellular tyrosine kinases and protein kinase C, increasing intracellular calcium. This cascade degranulates mast cells and basophils with subsequent release of histamine, tryptase, and chymase, which comprise the “early phase” of the reaction and begins transcription of specific cytokines (eg, interleukin [IL]-1, -2, -5, -6, -8, -9, -13), chemokines, and growth factors (eg, vascular endothelial growth factor) that initiate the “late-phase” reaction.⁹ Histamine binds to selective H1-receptors, inducing vasodilation and increasing blood flow and vascular permeability of the submucosal or subcutaneous capillaries, and/or postcapillary venules. Vessel leakage is dependent on the integrity of the endothelial cell-cell junction and cell-surface expression of the transmembrane adhesive protein, vascular endothelial (VE) cadherin. Histamine also phosphorylates VE-cadherin, which weakens this tight barrier.^{10,11} In addition, histamine stimulates nitric oxide expression, increasing blood

flow.¹² The net result is increased plasma extravagation to nearby tissues, producing angioedema. The underlying mechanism of IgE-dependent angioedema and urticaria is the same; the former occurs in deeper levels of the dermis and subcutaneous tissues, whereas the latter occurs in the superficial papillary and middermis layers. Pruritus is the result of histamine-stimulated afferent type-C fibers and the release of substance P.

There are multiple downstream effects of mast cell and basophil activation. For example, several cell types, including neutrophils, eosinophils, macrophages, basophils, and CD4+ T cells, form a nonnecrotizing infiltration into local tissue.¹³ This pathology differs from urticarial vasculitis in which there is vessel wall necrosis.^{14,15} Activation of neutrophils may further increase vascular leak through release of leukotriene B4.¹⁶

Nonallergic Mast-Cell-Mediated Acute Angioedema

Presentation

Acute urticaria and angioedema occur less frequently from direct mast cell activation or a non-IgE-mediated process. These triggers include some medications and infections, but more frequently, the cause remains unidentified. Depending on the inciting event, some reactions can occur within 1 hour after exposure to the precipitant, for example, drugs (eg, opiates, vancomycin, nonsteroidal anti-inflammatory drugs [NSAIDs] [see Cosby Stone and Nancy J. Brown's article, "[ACE-Inhibitor and Other Drug-Associated Angioedema](#)," in this issue]), or radiocontrast dye. Bacterial, viral, parasitic, or fungal pathogens such as *Helicobacter pylori*, Streptococci, Staphylococci, *Giardia lamblia*, *Mycoplasma pneumoniae*, hepatitis virus, Norovirus, Parvovirus B19, Anisakis simplex, and *Entamoeba* ssp have been implicated as underlying causes, but are not routinely screened for as a cause.³ Respiratory tract infections are most commonly reported in children with symptoms of acute urticaria and angioedema, but may also be a trigger in adults.^{17–19}

Pathophysiology

Although mast cells are typically activated by cross-linking of their FcεRI and IgE-Ag complexes, there are alternative pathways. Anaphylatoxins C3a and C5a, the human antibacterial peptide B-defensin, and substance P degranulate mast cells.^{20–22} In addition, murine studies have demonstrated that influenza A-specific IgG2_a, IgG2_b, and IgG₁ induced mast cell degranulation.²³ After mast cell activation, the subsequent inflammatory cascades are similar to IgE-triggered events.

CHRONIC ANGIOEDEMA

Histamine-Mediated Angioedema with Chronic Urticaria

Angioedema is present in approximately 40% to 50% of patients with chronic urticaria (CU).^{24,25} The following section focuses on the classifications of CU, based on 2 guidelines: the EAACI/GA²LEN/EDF/WAO³ and the JFT,⁴ which share many similarities, but differ on some recommendations. Persistent symptoms greater than 6 weeks is a widely agreed upon definition of CU. However, the frequency of symptoms per week is not listed in either guideline, but most reports suggest that it should be present for at least 3 days per week.^{26–29} Both guidelines divide CU into 2 subtypes, but differ slightly in the terminology. The EAACI/GA²LEN/EDF/WAO groups CU into "inducible" urticaria (CIU), in which symptoms are secondary to specific triggers (ie, UV light, cold, exercise, pressure, water, vibration), and "spontaneous" urticaria (CSU), which develops without identifiable provocation³ (**Table 2**). The JFT uses the terminology "continuous" and "intermittent."⁴

Table 2
Classification of chronic urticaria with angioedema

Types	Subtypes	Eliciting Factors
Spontaneous	Chronic spontaneous urticaria	No identifiable trigger
Inducible		
Physical urticarias	Cold contact urticaria	Exposure of skin to cold air, cold objects, or cold liquids
	Delayed pressure urticaria	Vertical pressure and wheal development 30 min to 12 h after exposure
	Heat contact urticaria	Direct skin contact with a warm object
	Solar urticaria	Exposure of skin to sunlight of specific wavelength
	Symptomatic dermatographic urticaria	Mechanical stroking or scratching of the skin surface and wheal development 1–5 min after exposure
	Vibratory urticaria	Exposure to mechanical vibration
Other inducible urticarias	Aquagenic urticaria	Skin contact with water at any temperature
	Cholinergic urticaria	Elevation of body temperature with exercise, hot water, strong emotion, or spicy food
	Exercise-induced anaphylaxis/urticaria	Exertional activity

Physical Urticaria

Presentation

The physical urticarias are a heterogeneous subgroup in which wheals are reproducibly induced by specific physical stimuli, such as mechanical pressure (ie, rubbing, vibration), thermal stimuli (ie, cold, heat), or sunlight.^{30,31} Approximately 25% of patients with CU demonstrate symptoms consistent with physical urticaria, most frequently in young adults.³¹ Physical urticaria may be present in children, but it occurs less frequently than in adults.³²

The severity of physical urticaria varies and may depend on the subtype, and in some cases, may be potentially life threatening (ie, airway swelling after a cold exposure in patients with cold induced urticaria). Angioedema is usually limited to the stimulus site; however, generalized symptoms can occur. Dermographism is the most common form of physical urticaria, which presents with raised urticarial wheals on the site of the skin after scratching or stroking (termed “simple dermographism”) or extensive wheals in areas extending beyond those which were stimulated (termed “symptomatic dermographism”).³³ Triggers of dermographism include itching dry skin, resulting in linear urticarial lesions, and rubbing of clothing, or direct pressure upon the skin (for example, sitting on a chair). Delayed-pressure urticaria/angioedema, occasionally classified as a subtype of symptomatic dermographism, is an erythematous swelling of the skin developing approximately 4 to 6 hours after application of pressure. Its causes are similar to those producing dermographism, including sitting for prolonged periods of time, tight clothing, or carrying heavy bags. Vibratory angioedema is the development of pruritus with subsequent angioedema (usually without urticaria) after exposure to a vibratory stimulus.^{34,35} Triggers include mowing the lawn,

bicycle riding, or jack-hammering. Other less common causes of physical urticaria include local heat, in which there is direct contact of the skin with a warm stimulus, and aquagenic urticaria, secondary to contact with water of any temperature, with symptoms developing ~20 to 30 minutes after exposure.

Pathophysiology

The underlying pathophysiologies of the physical urticaria/angioedema are not completely understood, but likely involve mast-cell stimulation with release of its vasoactive mediators, much like nonallergic acute angioedema/urticaria. Mast cell involvement is suggested by increased serum histamine in patients with dermatographism or aquagenic urticaria.^{36–40} In addition, increased IL-1 and IL-17 expression^{41,42} and activation of blood coagulation and fibrinolysis (demonstrated by increased platelet activation and increased D-dimer)^{43,44} contribute to the underlying pathogenesis of delayed pressure urticaria/angioedema.

Cholinergic Urticaria

Presentation

Cholinergic urticaria is characterized by numerous small (1–3 mm) punctuate wheals surrounded by large flares. Lesions typically originate in the trunk. Cholinergic urticaria is often associated with increased body temperature secondary to hot water, exercise, and sometimes strong emotions and spicy foods. Cholinergic urticaria can present with cholinergic urticaria with angioedema, but this does not occur commonly. However, recently a group of patients developing cholinergic urticaria with angioedema, most commonly around the eyelids, and some with anaphylaxis, after exercise or bathing in hot water were identified.⁴⁵

Pathophysiology

Acetylcholine (ACh) stimulation is thought to be an underlying cause of cholinergic urticaria, as demonstrated by patients developing local urticaria after ACh injection.⁴⁶ Some patients appear to have an IgE-mediated reaction to their sweat,⁴⁷ whereas others appear to have a non-IgE-mediated mechanism through modification of their ACh receptor, especially in those with concomitant hypohidrosis.⁴⁸

Chronic Spontaneous Urticaria with Angioedema

Presentation/pathophysiology

The presentation of CSU is similar to that of CIU, except that there is no identifiable trigger. Similar to CIU, a lowered mast cell activation threshold is central to the underlying pathophysiology of CSU. However, the exact trigger of mast cell degranulation in CSU is not clear. In approximately one-third of patients, there are IgG autoantibodies targeted to either IgE or the α subunit of the high-affinity IgE receptor (Fc ϵ RI α), which then activates mast cells and basophils.^{49,50} Although IgE sensitization does not play a role in the pathogenesis of CSU, skin biopsies of patients have demonstrated an eosinophilic and T helper 2 cellular infiltrate. This may be due to activation of the innate pathway, through release of IL-25, IL-33, and thymic stromal lymphopoietin by stromal cells, including endothelial and epithelial cells.⁵¹ In vitro studies have also suggested activation of the classical complement pathway.^{52,53} In some patients, there is evidence of systemic inflammation as demonstrated by increased plasma IL-6, which may correlate with disease activity.^{54,55}

It is postulated that a proportion of CSU patients might have underlying emotional stress as an exacerbating factor, but it is unlikely to be the sole cause of disease.^{16,56,57} Previous studies have reported that half of patients with CSU experience

high rates of anxiety, depression, and somatoform disorders.^{58,59} However, it is important to note that CU also induces emotional stress and produces a substantial negative impact on the quality of life for patients.⁶⁰ Therefore, there is likely an important bidirectional relationship between urticaria and emotional stress.

Histamine-Mediated Angioedema Without Urticaria

Presentation

A focus of the 2014 HAWK conference was to classify angioedema without wheals.² At this meeting, the term *idiopathic histaminergic acquired angioedema (IH-AAE)* was developed to describe patients who develop recurrent episodes of angioedema without urticaria, whose symptoms are controlled by antihistamines and in whom there is no identifiable cause such as allergy or physical stimuli.² The prevalence of IH-AAE is not well established, possibly due to its recent terminology. However, in a large referral center for angioedema, 379 of the 1058 consecutively referred patients for angioedema without urticaria over a 10-year period had chronic angioedema without cause that responded to antihistamine therapy, thus fulfilling the definition of IH-AAE.⁶¹ This group of patients typically present with angioedema developing rapidly, reaching its maximum swelling by 6 hours, and resolving within 24 hours. The face is the most commonly affected body site, but it may involve the extremities and GI mucosa (in <30% of patients). Although it may be present in patients of all ages, it is typically detected in those between 36 and 42 years of age.⁶² In children, histaminergic angioedema without urticaria can occur, but is less common than in adults.⁶³

DIAGNOSIS AND EVALUATION

Acute Angioedema

A directed patient history is critical to determine whether angioedema may be histamine or bradykinin mediated (see [Table 1](#)). Patients should be asked if they have ingested foods before symptoms onset, with particular attention to those more commonly allergenic (eg, peanut, tree nuts, fish, shellfish in adults, and milk and egg in children). An IgE-mediated reaction typically occurs within 1 hour after ingestion and can be later assessed by skin prick testing or serum evaluation for food Ag-specific IgE. Medication history should address recent use of antibiotics, NSAIDs, or ACE-I. Not all medication-related angioedema or urticaria episodes are IgE mediated. Commonly, IgE-mediated reactions to antibiotics are from penicillins, for which IgE evaluation has been established.⁶⁴ Many other medication reactions producing angioedema/urticaria are not IgE mediated, such as NSAIDs; therefore, skin prick testing or serum evaluate is not helpful. ACE-I-induced angioedema is bradykinin mediated. Routine blood work (ie, complete blood cell counts, complete metabolic panels) testing in acute urticaria is not indicated.³ The occurrence of urticaria with angioedema favors a histamine-mediated process. However, the nature of the urticarial lesions should be assessed for their duration and response to antihistamines in order to exclude other causes, such as urticarial vasculitis, as mentioned previously. In addition, the patient's response to antihistamines, corticosteroids, or epinephrine is an important clue to suggest a histamine-driven disorder, whereas a lack of response suggests a bradykinin-mediated process.

Chronic Angioedema

The underlying cause of chronic histamine-mediated angioedema is rarely determined. As a result, extensive laboratory testing is not recommended by the EAACI/GA²LEN/EDF/WAO and JTF guidelines.^{3,4} Both recommend a complete blood cell count with differential, complete metabolic panel, and erythrocyte sedimentation rate

or C-reactive protein (to exclude the possibility of an underlying chronic condition that could be treated). The JTF guideline also recommends a thyroid-stimulating hormone test and liver function enzymes test. Although many patients with CSU may have an underlying autoimmune component, its evaluation is not recommended because it does not change the choice of therapy. Antibodies that are commonly detected include antithyroid antibodies and IgG autoantibodies against the high-affinity IgE receptor (FcεR1) or IgE; the presence of the latter autoantibodies often results in a positive autologous serum skin test (ASST).⁶⁵ The incidence in an autoimmune component in children is not well established. However, a single-site retrospective study of 100 children (ages 0.7 months to 17 years), evaluated for CSU over a 7-year period, noted that 46.7% had a positive ASST.⁶⁶

The natural history of CU is difficult to predict, and the duration of symptoms varies. Some patients may have a 30% to 50% remission rate within 3 years after symptom onset,^{67,68} whereas others remain symptomatic 10 years beyond their initial presentation.⁶⁹ However, there are several factors that can aid in prediction of prognosis. Patients who experience urticaria with angioedema appear to suffer symptoms longer than those with urticaria alone,⁷⁰ or those with angioedema alone.^{57,68} Patients with milder disease, compared with those with moderate to severe symptoms, tend to have a shorter symptom duration.^{70,71} Furthermore, patients with a component of auto-reactivity (ie, positive ASST or antibodies against FcεR1 or IgE) tend to have a longer duration of disease than those without.^{72,73} Finally, the presence of physical urticaria with other forms of angioedema/urticaria often prolongs duration of disease.^{68,71,74}

Differential Diagnosis

Besides distinguishing histaminergic angioedema from bradykinin-mediated angioedema, which can be suggested by urticaria in the former, and a lack of response to antihistamines and corticosteroids in the latter, there are other disorders that can present with urticarial-like lesions and angioedema. Examples include mastocytosis (which can present with pigmented papules), urticarial vasculitis, and systemic lupus erythematosus. Cryoglobulinemia may cause cold-induced urticarial or vasculitic lesions in patients with hepatitis B or C. Gleich syndrome is episodic angioedema with eosinophilia. Hypereosinophilic syndrome is a group of disorders due to increased production of eosinophils with tissue deposition, resulting in a variety of symptoms depending on the subtype, which can include recurrent urticaria and angioedema. The Muckle-Wells syndrome is rare, but involves mutations in cryopyrin, and patients may have periodic urticarial eruptions and persistent swelling (potentially due to amyloid deposition). Patients also experience sensorineural hearing loss and arthritis. In addition, angioedema must be distinguished from edema, either protein-losing conditions or cardiac failure. Unlike angioedema, edema is pitting, typically symmetric (ie, both extremities), and in dependent areas of the body. Obstructive abnormalities such as superior vena cava syndrome or head and neck tumors may present with persistent swelling.

MANAGEMENT

Acute Management

An acute episode of angioedema/urticaria can occur as the initial episode or as a flare of chronic disease. If patients require an emergency room visit for their symptoms, the evaluation must first address their airway for potential asphyxiation due to airway edema. Evaluation includes monitoring physical symptoms which may suggest airway compromise such as change in voice, difficulty swallowing, or stridor.⁷⁵ If there are

signs of significant airway compromise, intubation should be considered. Next, the patient's vital signs should be accessed for hypotension and tachycardia, which occur due to profound vasodilation and increased vascular permeability, producing fluid shifts. After the patient's airway and hemodynamic status are evaluated and stabilized, the history and physical examination should distinguish between histamine- and bradykinin-mediated angioedema (see [Table 1](#)), which will guide subsequent management. Unfortunately, at the present time, there are no blood tests to provide rapid results to help determine the underlying mediator (eg, histamine vs bradykinin); therefore, the history is critical. In addition, measurement of histamine and bradykinin in the serum is difficult to perform and not commercially available. However, certain laboratory work can be performed, such as serum tryptase (elevated in mast-cell activation) and C4 (decreased in HAE type I and II, and acquired C1-INH deficiency; see Iris M. Otani and Aleena Banerji's article, "[Acquired C1 Inhibitor Deficiency](#)"; and Kaplan AP and Joseph K's article, "[Pathogenesis of Hereditary Angioedema: The Role of the Bradykinin Forming Cascade](#)," in this issue), which can be followed up on upon discharge. Performing serum Ag-specific IgE testing during an acute episode does not provide rapid results either and should be done approximately 2 or more weeks after the episode for most reliable results. If the patient has been previously evaluated for angioedema/urticaria, it is more likely that the underlying mediator producing symptoms has been established.

The following section briefly discusses additional measures in acute management of angioedema/urticaria. However, the reader is referred to recently published summary statements on the management of angioedema in an emergency room for a detailed discussion on the approach and treatment of patients with acute angioedema in this setting.^{75,76} The treatment of histamine-mediated acute angioedema and urticaria is directed by its symptoms. For patients presenting with airway compromise and/or a systemic reaction (ie, hypotension, tachycardia, GI symptoms), intramuscular epinephrine is required and can be repeated every 5 to 15 minutes as needed.⁷⁵ Antihistamines are also administered during an acute histamine-mediated episode of angioedema/urticaria of any severity. Only first-generation antihistamines (ie, diphenhydramine) are available for intravenous administration, but second-generation antihistamines, only available in oral preparations, are equally effective. Glucocorticoids are often administered to prevent late-phase reactions that can occur 4 to 6 hours after the initial response. In cases in which patients have required epinephrine, they must be prescribed and taught how to use a self-injectable epinephrine before discharge. Patients should also be referred to an allergist upon discharge who can follow up for evaluation of IgE sensitizations and continued management. If the allergic trigger is identified during the emergency visit, the patient must be educated to avoid it upon discharge.

Chronic Management

The preventive management of histaminergic angioedema is extrapolated from the management of CU. The first-line therapy is second-generation, nonsedating antihistamines. There are no preferred antihistamines, and all theoretically should work equally well; therefore, the drug selection must be based on a discussion between the patient and physician. Some patients report an improved response to certain antihistamines, or tolerate specific preparations, or there may be a cost issue. The initial daily dose to administer antihistamine may be at the standard dose, or in some patients, higher based on their severity of symptoms (ie, twice a day). At the initial treatment, any triggers of symptoms should be avoided. However, it is not necessary to recommend that patients avoid all potential triggers of angioedema/urticaria if they have not experienced symptoms with their exposure (eg, asking all patients with urticaria to avoid NSAIDs if they

have previously tolerated them). If patients have persistent symptoms after a 2-week daily preventative antihistamine treatment, the next step is to titrate the dosage up to a maximum of 4-fold the standard labeled dose.³² The JFT guidelines also recommend the addition of H2-blockers, first-generation antihistamines before bed, and leukotriene-modifying agents if 4 times a day dosing is not completely effective.^{4,77} However, first-generation antihistamines present the risk of increased sedation, which is particularly problematic for older patients.³ A short course of oral corticosteroids may be considered in these patients; topical corticosteroids are typically of little benefit. If symptoms persist despite these measures, the addition of omalizumab (Xolair, Genentech, Inc, San Francisco, CA, USA), an anti-IgE antibody, can be considered. Omalizumab has strong data suggesting its efficacy in CU and is approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of adults and adolescents who have refractory CIU and CSU.⁷⁸ Case reports suggest that it improves physical urticarias, including solar, cold, delayed pressure, dermatographism, and cholinergic urticaria as well as idiopathic histaminergic angioedema.^{79–81} Importantly, it has also been demonstrated to significantly improve quality of life of patients with urticaria.⁸² In addition to omalizumab, cyclosporine A (CsA) should be considered. Before the availability and approval of omalizumab, CsA was often used with improvement of symptoms. However, CsA is an immunosuppressant and is frequently associated with adverse effects, including GI disturbances, elevated blood pressure, and possible nephrotoxicity, limiting its use. Additional anti-inflammatory and other immunosuppressants, such as dapsone, sulfasalazine, hydroxychloroquine, colchicine, anti-tumor necrosis factor- α , and the anti-CD20 biologic, rituximab, have shown improvement in smaller, less rigorous studies of patients with CU and are therefore not frequently prescribed.^{4,83,84} If the treatment with high-dose antihistamines and alternative agents does not improve symptoms, an alternative diagnosis should be considered, including evaluation for a bradykinin-mediated process.

The optimal duration of therapy for chronic histamine-mediated angioedema/urticaria is unknown. Providers should consider tapering therapy once patients have achieved complete symptom control to assess for disease remission. Fortunately, there are few adverse effects with long-term second-generation antihistamine use. Omalizumab can be reduced in frequency of interval injections from every 4 weeks to every 6 weeks or longer with continued monitoring for symptom recurrence.⁷⁷

SUMMARY

Histaminergic angioedema is the most common form of angioedema and must be distinguished from bradykinin-mediated forms for optimal treatment. Histaminergic angioedema is frequently associated with urticaria. It is classified upon its duration of symptoms into either acute or chronic. Evaluation for an IgE-mediated process is indicated in the evaluation of acute angioedema/urticaria. Chronic angioedema/urticaria may be classified as inducible or spontaneous forms, based on its trigger or lack of known trigger, and can occur in the presence or absence of urticaria. Unfortunately, the underlying trigger of CU is frequently not able to be determined, and bothersome symptoms may persist for several months to years. Consequently, this disorder has a significant negative impact on patients' quality of lives. The mainstay of treatment of histaminergic angioedema/urticaria is second-generation antihistamines to prevent symptoms (chronic cases) as well as for treatment of acute attacks. All patients with previous episodes of airway angioedema from a histamine-mediated process must be prescribed and taught how to self-inject epinephrine and be educated on its indications for use.

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