

The Clinical Evaluation of Angioedema



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KEYWORDS

• Angioedema • Bradykinin • Histamine • Hereditary angioedema

KEY POINTS

- Angioedema may occur through several mechanistic pathways. An understanding of the pathophysiology aids in the evaluation, clinical diagnosis, and management of this condition.
- Angioedema can be broadly categorized into episodes occurring with or without urticaria; after this distinction is made, this allows for the further differentiation of angioedema subtypes.
- The initial step in the clinical evaluation of angioedema is obtaining a thorough patient and family history, while giving consideration to differential diagnoses and angioedema mimickers.
- Although episodes of angioedema without urticaria may be clinically similar in presentation, there are characteristics and laboratory parameters that are unique to each subtype. Applying an algorithmic approach based on these parameters allows one to reach an accurate diagnosis.
- Further research in the clinical evaluation of angioedema directed at developing a greater understanding of the pathophysiology should enable the development of new diagnostic assays and novel targeted treatments.

INTRODUCTION

Angioedema, also known as Quincke edema or “angioneurotic edema,” was first described by Marcello Donati in 1586 in reference to a young count who developed lip swelling as a result of an egg allergy.¹ The first reference to hereditary angioedema resulting in fatal suffocation was reported by Osler in 1885.²

It is estimated that up to 25% of the US population will experience an episode of urticaria with or without angioedema during their lifetime.³ Angioedema is defined

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as the localized nonpitting edema of deep dermal, subcutaneous, or submucosal tissues resulting from the increase in vascular permeability and extravasation of intravascular fluids; although it can coincide with urticaria in a histamine-mediated process, a differentiating feature is that urticarial wheals are limited to the mid and papillary dermis.³

This article serves as a general overview of the clinical evaluation of angioedema with and without urticaria and focuses on the following:

1. Signs and symptoms of angioedema
2. Classification of angioedema subtypes
3. Pathophysiology
4. An approach to the clinical evaluation of angioedema
5. Diagnostic evaluation in angioedema
6. Future directions in the evaluation of angioedema

More detailed discussion about angioedema mechanisms and treatments will be presented in other sections of this issue of *Immunology and Allergy Clinics of North America*.

SIGNS AND SYMPTOMS OF ANGIOEDEMA

The presentation of angioedema may vary between subtypes, although in all forms, it can occur at any site of the body and some organ tissues. The edema itself is non-pitting, typically with ill-defined borders, and may be flesh-colored or erythematous in nature. Episodes of swelling may be accompanied by pruritus and urticaria, in the case of histamine-mediated forms, or associated with a burning and tingling sensation.

The most commonly involved sites include the following:

1. Head and neck: Angioedema affecting the eyelids, lips, tongue, and larynx, with the possibility of life-threatening airway obstruction
2. Peripheries: Swelling of the hands, feet, and urogenital areas
3. Abdomen: Angioedema may mimic symptoms of an acute abdomen, resulting in surgical intervention

Examples of these site-specific swellings are depicted in [Fig. 1](#) and [Fig. 2](#).

Several factors are known to increase the probability as well as the severity of specific angioedema subtypes as discussed later, but can include foods and medications resulting in direct mast cell degranulation (ie alcohol, non-steroidal anti-inflammatory drugs [NSAIDs]), stress, dental or surgical manipulation, and hormonal factors.^{4,5}

PATHOPHYSIOLOGY OF ANGIOEDEMA

Acute episodes of angioedema result from a release of vasoactive mediators that increase vascular permeability in the skin and submucosa, allowing for the vascular leakage of plasma and resultant edema; most of these attacks can be attributable to the following.

Histamine-Mediated Pathways

Immunoglobulin E (IgE)-mediated reaction begins with a primary response and typically occurs within seconds to minutes of exposure to an allergen, from the release of vasoactive amines such as histamine, and results in increased vascular permeability, smooth muscle contraction, vasodilation, glandular secretions, and bronchospasm.⁶

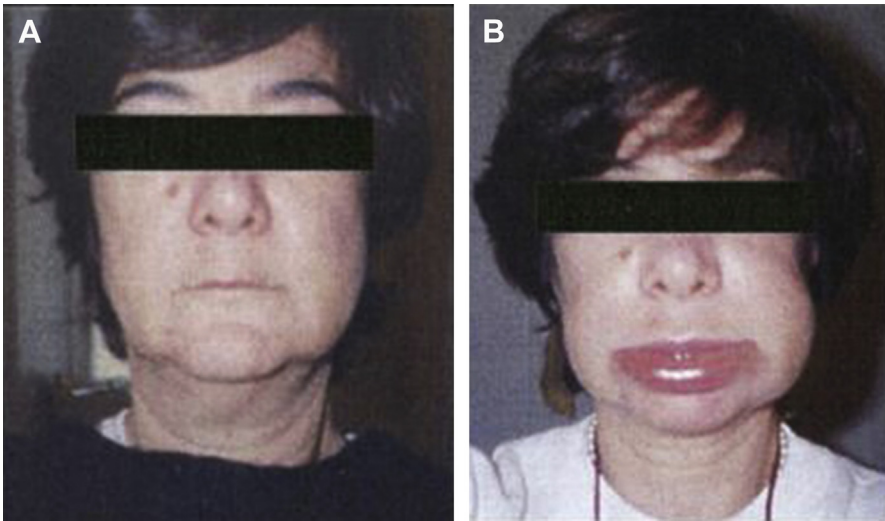


Fig. 1. Patient with angioedema affecting her lips: a comparison between (A) baseline and (B) during an attack. (*Adapted from* Bowen T, Cicardi M, Farkas H, et al. Canadian 2003 International Consensus Algorithm for the diagnosis, therapy, and management of hereditary angioedema. *J Allergy Clin Immunol* 2004;114(3):631; with permission.)

The secondary, or late phase response, occurs 8 to 12 hours after allergen exposure and results from the synthesis of leukotrienes, chemokines, prostaglandins, and platelet-activating factor (**Fig. 3**).⁷ The late phase response results in tissue infiltration by leukocytes, specifically eosinophils, resulting in an inflammatory response and the production of leukotrienes and prostaglandins.⁶

There may be an association with autoantibodies directed against the Fc-epsilon receptor (FcεR) of both the mast cell and the IgE molecules, resulting in histamine release and the development of urticaria and angioedema.⁸ The high-affinity form of this receptor, FcεR1, plays a significant role in allergic diseases, in addition to the production of inflammatory mediators.⁹ This mechanism can be demonstrated through the use of an autologous serum skin test, where the intradermal injection of one's own serum results in a wheal and flare response.¹⁰

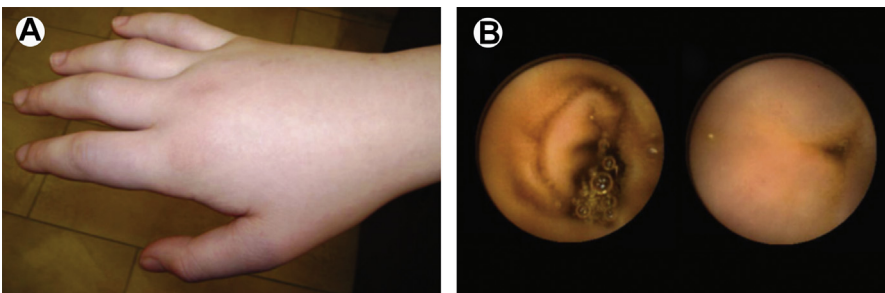


Fig. 2. (A) Angioedema of the hand in a patient with hereditary angioedema. (B) Capsule endoscopy during abdominal attack in patient with hereditary angioedema, showing ileal tract with normal mucosa and lumen (*left*), and edematous ileum and substantially reduced lumenal diameter, causing partial bowel obstruction (*right*). (*From* Longhurst H, Cicardi M. Hereditary angio-oedema. *Lancet* 2012;379(9814):475; with permission.)

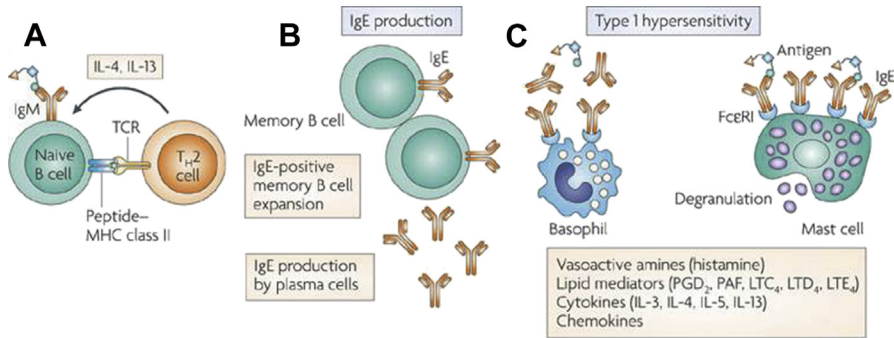


Fig. 3. (A) TH2 cell interaction with naive B cells leads to immunoglobulin class switch to IgE and expansion of allergen-specific memory B cells. (B) IgE produced by plasma cells sensitizes mast cells and basophils by binding to surface FcRI. (C) The crosslinking of basophil and mast-cell surface FcRI-bound IgE by B-cell epitopes of allergens leads to the release of vasoactive amines (such as histamine), lipid mediators (such as prostaglandin D2 [PGD₂], platelet-activating factor [PAF], leukotriene [LT] C₄ [LTC₄], LTD₄ and LTE₄, cytokines and chemokines), and to the immediate symptoms of allergic disease (type I hypersensitivity), including pruritus, wheal and flare, nasal conjunctival discharge, angioedema, systemic anaphylaxis, and bronchoconstriction. T-regulatory (TReg) cells modulate type-1 hypersensitivity reactions by suppression of IgE and induction of blocking antibodies by interleukin-10 (IL-10), suppression of mast-cell tissue infiltration by IL-10 and transforming growth factor (TGF), and suppression of TH2 cells by IL-10 and TGFβ. MHC, major histocompatibility complex; TCR, T-cell receptor. (From Akdis M, Akdis CA. Therapeutic manipulation of immune tolerance in allergic disease. *Nat Rev Drug Discov* 2009;8(8):650; with permission.)

Bradykinin-Mediated Pathways

In the case of hereditary, acquired, or angiotensin-converting enzyme inhibitor (ACE inhibitor) -induced angioedema, the vasodilatory peptide, bradykinin, plays a key role in endothelial cell activation, with resultant tissue edema.¹¹ Bradykinin is released from many cell types, and mechanisms that interfere in either its production, or as in the case of ACE inhibitors, its degradation, result in angioedema.

Angioedema may occur through several mechanisms as outlined in later discussion, namely, the complement, coagulation, and contact pathways that are essential in the regulation of bradykinin.

C1-esterase inhibitor (C1-INH) is a member of the serine protease family (serpin), whose role it is to prevent the formation of the C1 complex and the consequent complement activation. It also acts as a direct inhibitor of activated kallikrein.¹¹ C1-INH also plays a regulatory role in fibrinolytic, coagulation, and kinin pathways.¹²

In hereditary angioedema type 1 and 2 (HAE-1 and HAE-2), there is a deficiency in an inhibitory enzyme of the complement system, C1-INH, which results in complement activation and kallikrein production, both contributing to the production of bradykinin (Fig. 4).¹³ C1-INH deficiencies also affect the complement pathway, fibrinolytic system, and the intrinsic coagulation pathways.

Mutations in the SERPING1 gene located on the eleventh chromosome result in decreased antigenic levels of C1-INH seen in HAE-1 or a functional impairment, as in HAE-2.⁴ Both are inherited in an autosomal dominant manner, although up to 25% of all cases may be due to spontaneous mutations.^{14–16} HAE-1 occurs in 86% of cases,¹⁶ whereas HAE-2 is less commonly identified (in up to 15% of cases); HAE-nC1INH is inherited in an autosomal dominant manner and occurs mostly in

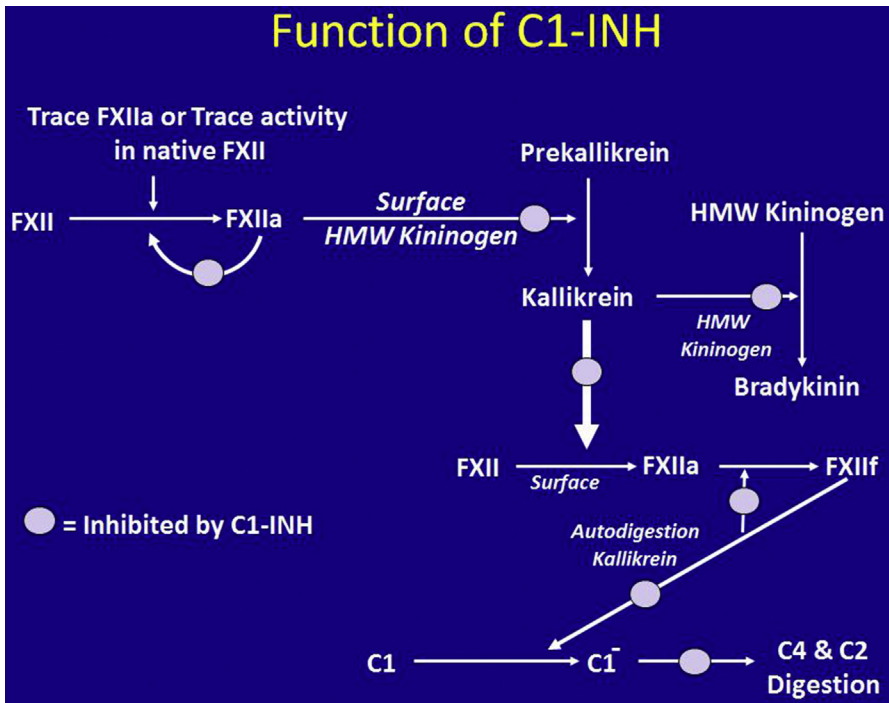


Fig. 4. Zinc-dependent binding of factor XII and HK to vascular endothelial cells. Although both bind to gC1qR, which is present in excess, there is preferential binding of factor XII to the complex of u-PAR and cytokeratin 1, while HK binds primarily to the complex of gC1qR and cytokeratin 1. HK, high-molecular-weight kininogen.

women. However, some male patients have been reported. In some cases, HAE-nC-INH may be associated with a gain of function mutation in Factor XII, resulting in kinin overproduction.¹⁴

Investigations into the role of the coagulation and contact pathway in angioedema have found that dysregulation of these processes may result in increased clotting activities of Factors XII, XI, and V. An in vitro diagnostic test, activated partial thromboplastin time (APTT), can be used as a surrogate marker of both the intrinsic and common coagulation pathways and the contact system. Recent research has shown that shortened APTT levels are seen in individuals with deficient levels and function of the C1-INH as well as in acquired forms of angioedema in comparison to angioedema with normal C1-INH.¹⁷

In the case of HAE-1, it is the level and function of C1-INH that are decreased, whereas in HAE-2, there is a normal level of C1-INH, but a functional deficiency. The pathophysiology of HAE-nC1INH is poorly understood, because there are no detectable abnormalities in the C1-INH, but has been associated with mutations in the Factor XII gene. Acquired causes of bradykinin-mediated angioedema have been associated with antibody production against the C1-inhibitor enzyme itself.^{6,11}

Further insights into the pathophysiology and mechanisms underlying these processes are addressed in later sections of this issue of *Immunology and Allergy Clinics of North America*, which are devoted to hereditary angioedema.

Angioedema Resulting Through Cyclooxygenase 1 Inhibition

Angioedema may arise as a consequence of the inhibition of cyclooxygenase 1 (COX-1), leading to unopposed arachidonic metabolism, with resultant leukotriene synthesis, as by NSAIDs. The net result of the accumulation of these vasoactive cysteinyl leukotrienes is an increase in vascular permeability, fluid extravasation, and resultant edema.¹⁸

Type III Hypersensitivity Reactions

A rarer cause of angioedema and urticaria results from the formation of antigen-antibody complexes through type III hypersensitivity reactions (as in the case of urticarial vasculitis).¹⁹

Table 1 summarizes the key differences in pathophysiologic mechanisms of angioedema subtypes.^{18,20,21}

CLASSIFICATION OF ANGIOEDEMA

The most common form of angioedema is the allergic type, followed by idiopathic and ACE-inhibitor induced. Hereditary and acquired forms are relatively rare in comparison.¹⁴ Angioedema can be classified into several subtypes, differentiated by the clinical presentation and pathophysiology:

1. Histaminergic (through IgE-independent or -dependent mechanisms)
2. Idiopathic
3. Hereditary angioedema (HAE-1, HAE-2, and HAE-nC1INH)
4. Acquired angioedema (including ACEi-induced and C1-INH deficiency)

APPROACH TO THE CLINICAL EVALUATION AND DIAGNOSTIC WORKUP

In addition to obtaining a thorough patient and family history of angioedema, the clinical presentation, time to the onset of symptoms, and recognition of differentiating characteristics are imperative in making an accurate diagnosis.

Histamine-Mediated Angioedema

Clinical features

Allergic angioedema The initial stratification of angioedema subtypes involves determining if these attacks are accompanied by pruritic urticarial wheals, which can be categorized as histamine-mediated or “allergic” angioedema, resulting from mast cell degranulation and the release of inflammatory mediators such as histamine in either IgE-dependent or -independent manners. Triggers may include foods, medications, latex, insect bites, and stings, for example.

In addition to angioedema, these reactions can manifest with a combination of one or more symptoms involving the respiratory, cardiac, neurologic, or gastrointestinal systems.³ Symptoms may include wheezing, coughing, chest pain or tightness, nausea, vomiting, lightheadedness, and even shock as a result of hypotension.

A differentiating feature of this form of angioedema is that it responds to treatment with corticosteroids, epinephrine, and antihistamines. Symptoms tend to be of shorter duration (typically <24 hours).³ Nonallergic forms of angioedema tend to worsen over the course of 24 to 36 hours and may last up to 3 to 5 days without appropriate treatment.¹³ Histaminergic angioedema can occur at various sites in the body, although in comparison to non-histamine-mediated forms of angioedema, it less commonly involves the genitalia.³

Table 1
Molecular mechanisms of angioedema

Type of AE	Mediator	Mechanism
Allergic AE	Histamine (mast cells)	Allergens react with IgE antibodies on the surface of mast cells, causing degranulation and release of histamine
ACE-I-induced	Bradykinin	ACE-Is prevent the conversion of bradykinin to inactive metabolites, leading to bradykinin accumulation
NSAID-induced AE	Leukotrienes (mast cells)	Inhibition of COX-1 leads to overproduction of vasoactive substances by shunting arachidonic acid metabolism through the lipoxygenase pathway, creating leukotrienes; vasoactive leukotrienes act on cell-surface receptors to increase vascular permeability and promote inflammation
HAE type 1	Bradykinin	Genetic mutations in the <i>C1 INH</i> gene result in low levels of C1 INH; major roles of C1 INH include inactivating coagulation factors XIIa. XIIa and XIa: blocking C1 complement autoactivation and inhibiting activated kallikrein; removal of these inhibitory actions results in complement activation and elevated bradykinin levels
HAE type 2	Bradykinin	Genetic mutations in the <i>C1 INH</i> gene result in normal levels of C1INH, but the C1 INH is dysfunctional; plasma cascades are unregulated in the presence of dysfunctional C1 INH, leading to bradykinin accumulation as in HAE type 1
Inherited AE with normal C1 INH	Bradykinin	Missense mutation in factor XII gene confers a significant increase in the protease activity of each activated factor XII molecule, which increases bradykinin generation; decreased activity of enzymes such as ACE and aminopeptidase P have also been noted
Acquired AE	Bradykinin	Type 1: Immune complex formation associated with rheumatologic, lymphoproliferative, and neoplastic disorders continuously activate C1, causing C1 INH depletion and bradykinin accumulation Type 2: Autoantibodies inactivate C1 INH, leading to bradykinin accumulation
Idiopathic recurrent AE	Unknown	Unknown

Abbreviation: AE, adverse events.

From Nzeako UC. Diagnosis and management of angioedema with abdominal involvement: a gastroenterology perspective. *World J Gastroenterol* 2010;16(39):4914; with permission.

Pseudoallergic angioedema Angioedema (with or without urticaria) developing after the use of NSAIDs may be either “pseudoallergic” or IgE mediated. Several subtypes of angioedema and urticaria with NSAID use have been identified²²:

1. NSAID-exacerbated angioedema or urticaria in up to 10% to 30% of those with underlying chronic urticaria.²³
2. NSAID-induced angioedema or urticaria in individuals without chronic urticaria.
3. Single NSAID-induced angioedema, urticaria, or anaphylaxis occurring in an IgE-dependent manner; these individuals may react to structurally related NSAIDs as well.

Idiopathic angioedema In a significant number of patients, no identifiable cause is found for recurrent episodes of angioedema with or without urticaria and is deemed

as “idiopathic” in nature once alternate identifiable causes have been excluded.²⁴ Idiopathic cases may occur in antibody-dependent and -independent mechanisms and typically respond to antihistamines and corticosteroids.¹⁴

In a study conducted by Zingale and colleagues²⁴ evaluating angioedema without urticaria, a specific cause was found in 16% of all patients (n = 776), and most of the cases were attributed to drugs, foods, and stings. Furthermore, in 7% of cases, an underlying disease process or infection was identified. ACE inhibitors contributed to 11% of all reactions, with a median time to onset of symptoms at 12 months after initiating therapy.^{24–26} Hence, it is important to evaluate for an underlying cause of angioedema before calling it idiopathic.

Consideration should be given to rare causes of angioedema if there is concern of an underlying autoimmune condition, malignancy, or inflammatory condition because the evaluation may require additional testing. Similarly, if the patient’s history and clinical presentation are atypical of either a histaminergic- or bradykinin-mediated process, one must rule out common mimickers.

DIAGNOSTIC EVALUATION OF HISTAMINE-MEDIATED ANGIOEDEMA

In cases of “allergic” and “pseudoallergic” angioedema, the clinical history aids in determining whether further diagnostic testing is required. In the case of specific triggers, such as foods, medications, bites or stings, skin prick testing, the use of specific IgE measurements, and oral challenges to foods and medications may be useful in identifying the culprit. A serum tryptase level and urine histamine levels are useful markers in that they may be elevated in acute episodes of histamine-mediated angioedema and urticaria.³ To note, in histaminergic angioedema, serum complement levels as well as C1-INH antigenic and functional levels are unaffected.

There are several additional investigations that may be useful in the evaluation of angioedema, both with and without urticaria. Investigations should be geared toward differential diagnoses and mimickers and may be useful in the workup of idiopathic or acquired forms of angioedema (Table 2).

If an underlying hematologic cause such as multiple myeloma or malignancy is of concern, a complete blood count with smear and differential may identify cytopenias, and a serum protein electrophoresis with immunofixation can be used to identify clonal immunoglobulin populations. A targeted malignancy workup (ie with imaging and biopsies) can also be pursued if there are organ-specific symptoms.

If autoimmunity or an inflammatory process is suspected, screening tests to consider would include an antinuclear antibody (ANA), rheumatoid factor, and inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, all of which may be elevated in these conditions. Furthermore, positive thyroid antibodies have been shown to be associated with chronic spontaneous urticaria, although their significance in the disease process is not well established.

In cases of immunodeficiencies associated with urticaria or angioedema, such as Gleich syndrome presenting with elevated IgM, angioedema and eosinophilia, quantitative immunoglobulins (IgA, IgG, and IgM), CH50, C3 levels, and immunoassays can be considered.

In ruling out angioedema mimickers related to infectious processes such as cellulitis, consideration may be given to obtaining blood and tissue cultures, in addition to skin biopsies. As peripheral edema secondary to impairments in the circulatory or lymphatic symptoms may resemble angioedema, electrolytes including renal function and a urinalysis may be helpful in identifying hypoalbuminemia and proteinuria.

Table 2
Summary of additional investigations to consider in the workup of acquired and idiopathic angioedema

Diagnostic Test	Significance
Specific IgE levels, skin prick testing, and oral challenges to suspected foods/medications	To evaluate for IgE-mediated causes of urticaria and angioedema
Serum tryptase and urine histamine	To evaluate for histaminergic causes of urticaria and angioedema
Complete blood count with smear and differential	To evaluate for cytopenias and hematologic malignancies
Serum protein electrophoresis with immunofixation	To evaluate for clonal populations, such as in multiple myeloma
Targeted malignancy workup	In the case of idiopathic or acquired forms
Quantitative immunoglobulins (IgG, IgA, IgM)	To evaluate for immunodeficiencies and conditions associated with urticaria and angioedema (ie, Gleich syndrome with elevated IgM, angioedema, and eosinophilia)
CH50, C3, and immune complex assays	To screen for associated complement deficiencies
Inflammatory and autoimmune markers: ESR, CRP, ferritin, rheumatoid factor, ANA	May be elevated in the case of autoimmune causes or inflammatory conditions
Thyroid function and antibodies	Associated with chronic spontaneous urticaria and autoimmune disease
Cultures (blood, tissue, throat, and urine) and infectious workup	To rule out infection or cellulitis as a mimicker or cause
Urinalysis and electrolytes	May identify proteinuria and hypoalbuminemia as causes of edema

During acute attacks, if organ involvement is considered, imaging studies such as radiographs, ultrasounds, and computed tomographic scans may be useful in identifying soft tissue swelling of the neck, ascites, and edema of the gastrointestinal tract.²⁷

If no confirmatory diagnosis can be made on the basis of these investigations, a trial of empiric therapy with antihistamines, corticosteroids, and epinephrine can be considered in the evaluation of histaminergic angioedema.

Bradykinin-Mediated Angioedema

Clinical features

Hereditary angioedema Hereditary angioedema is estimated to affect 1 in 10,000 to 1 in 50,000 individuals.²⁸ Patients may present with angioedema affecting many organ systems in an asymmetric distribution, including involvement of the head and neck, with concerns of life-threatening laryngeal attacks that may result in asphyxiation as well as swelling of peripheral tissues, urogenital edema, and abdominal pain. In up to 50% of cases, these attacks may be preceded by a tingling sensation or erythema marginatum, with nonpitting angioedema that is nonpruritic in nature.³

The severity of these attacks is variable and related to a multitude of exacerbating factors and triggers, such as dental and surgical manipulation, stress or trauma, menses, medications, and infections. Attacks can be precipitated by estrogen in particular, either through endogenous increases during menses or pregnancy or via exogenous sources, such as oral contraceptives or hormone replacement therapy.²⁹

It is estimated that up to 50% of HAE attacks may be precipitated by trauma or stress, although others may be spontaneous in nature.³⁰ Symptom onset typically begins in early life, with up to 75% of patients experiencing their first attack before the age of 15.¹⁴

HAE-1 constitutes approximately 80% to 85% of all cases of HAE. The swelling may present early in life, often by the teen years, and can increase after puberty. Like other causes of angioedema, episodes may be precipitated by physical or emotional stressors. HAE-2 represents 15% to 20% of all HAE cases and is similar in presentation to HAE-1. Angioedema may present in the face, extremities, abdomen, and other organ systems, with the concern of laryngeal edema and asphyxiation, as in the case of HAE-1.

The most common presentation is that of nonemergent angioedema resulting in impairment in quality of life with discomfort, immobility, and disfigurement, and the inability to attend work or school.³¹

Abdominal attacks occurring in up to 93% of patients with HAE²⁹ can present with mild to severe spasmodic pain and may be associated with gastrointestinal upset and even intestinal obstruction; hypovolemic shock may result from the extravasation of fluids.³⁰ These attacks can often be confused with appendicitis or cholecystitis, resulting in unnecessary surgical interventions,^{18,20} and even psychiatric referrals.⁴

Laryngeal attacks with respiratory impairment and the risk of asphyxiation is the most feared complication of these attacks, because these patients may require intubation and even tracheotomies.³⁰ It is estimated that up to 50% of HAE patients will experience at least 1 laryngeal episode within their lifetime.²⁵

In distinguishing between angioedema with impaired C1INH (ie, HAE-1 and HAE-2) versus HAE-nC1INH, there are several clinical characteristics that allow for differentiation: In the case of angioedema with normal C1INH, patients are usually women, presenting in adulthood. These individuals will more frequently present with facial swelling, specifically of the tongue, with the risk of asphyxiation and laryngeal involvement. In cases of HAE-nC1INH, there tends to be less abdominal involvement, and no antecedent erythema marginatum.³² Furthermore, the presentation and penetrance of the disease have been noted to be quite low, because patients have presented in later decades of life, with normal or low levels of estrogen.^{4,33,34}

Acquired agioedema Acquired forms of C1INH-deficiency, a bradykinin-mediated angioedema, typically present later in life in individuals with no family history of hereditary angioedema. It has been associated with lymphoproliferative and hematologic diseases. The estimated prevalence is reported to be 1:500,000,¹⁴ although it is thought to be underrecognized. Although the clinical presentation is similar to HAE, these individuals may present with additional symptoms of their underlying malignancy. Reduced antigenic and functional levels of C1-INH with low C4 complement levels (with a normal C3), in addition to having low levels of C1q, help distinguish acquired forms of angioedema from hereditary angioedema.¹⁴ Supporting evidence for acquired forms may be obtained from complete blood counts with lymphocyte immunophenotyping, blood films, inflammatory markers, antinuclear antibodies and complement levels, rheumatoid factor, and serum protein electrophoresis with immunofixation studies, as addressed in the consideration of diagnostic measures in the evaluation of idiopathic and acquired causes of angioedema. Consideration may also be given to bone marrow biopsies and targeted imaging studies to evaluate for underlying malignancies and lymphoproliferative disorders, such as lymphoma, multiple myeloma, and monoclonal gammopathy of uncertain significance, as a cause of acquired forms.^{5,12,35,36} Hereditary and acquired forms of C1 esterase inhibitor

(C1-INH) deficiency maybe difficult to distinguish clinically, although laboratory parameters and a family history of HAE aid in the differentiation between subtypes.

Angiotensin-converting enzyme-inhibitor induced angioedema It is estimated that 0.1% to 0.7% of patients on ACE inhibitors (and less commonly angiotensin receptor blockers) may develop angioedema,³⁷ typically occurring within the first week to month of treatment,³ although some cases may develop after years of therapy. Typical areas of involvement occur in the face, lips, and tongue with the risk of fatalities due to laryngeal involvement; in comparison to other angioedema subtypes, there is relative sparing of the gut and genital mucosa.⁵ Several risk factors have been identified, including prior head and neck surgery,³⁸ external trauma,³⁸ increasing age, and female gender, and even smoking.^{39–43} There is a preponderance among African Americans^{3,14} thought to be secondary to polymorphisms found in the aminopeptidase P gene, which plays an essential role in the metabolism of ACE inhibitors.³ There is no strong evidence to suggest that there may be a dose-dependent relationship nor has it been shown to occur with greater frequency with specific ACE inhibitors or with the timing of medications.⁴⁴

DIAGNOSTIC EVALUATION OF BRADYKININ-MEDIATED ANGIOEDEMA

To distinguish between hereditary angioedema subtypes, laboratory investigation begins with a screening measurement of a serum C4 complement level as well as obtaining diagnostic antigenic and functional levels of the inhibitor of the first component of the complement pathway, C1-INH. To note, as the sensitivity of a low C4 level in diagnosing HAE is estimated at approximately 86%,⁴⁵ pursuing further investigations with chromogenic assays to confirm diagnosis is recommended.

Both HAE-1 and HAE-2 are associated with decreased levels of C4 at baseline and during acute episodes; however, although HAE-1 is characterized by a low antigenic level of C1-INH, HAE-2 often has normal or even elevated antigenic levels of C1-INH with a functional impairment.³ HAE-nC1INH differs in that it maintains normal C4 complement levels with unaffected C1-INH antigenic and functional levels (Table 3).⁴⁶

In acquired forms of angioedema, the evaluation of complement levels, specifically C3, C4, and C1q, are useful markers because these are often reduced.³ In ACE-inhibitor induced and idiopathic bradykinin-mediated angioedema, the diagnosis is reliant on the clinical history because laboratory parameters, including serum complements, C1-INH antigenic and functional levels, serum tryptase, and urine histamine will all be normal.³

In cases of where angioedema is thought to be bradykinin mediated but investigations are normal and family history is negative, an empiric trial of treatment directed toward bradykinin-mediated angioedema could be considered.

Table 3 Laboratory findings in hereditary angioedema			
	C4	C1-INH Antigen	C1INH Function
HAE-1	↓	↓	↓
HAE-2	↓	Normal or ↑	↓
HAE-nC1INH			
FXII mutation	Normal	Normal	Normal
Unknown cause	Normal	Normal	Normal

From Betschel S, Badiou J, Binkley K, et al. Canadian hereditary angioedema guideline. Allergy Asthma Clin Immunol 2014;10(1):50; with permission.

Essential Components of the Clinical History

An accurate diagnosis is reliant on obtaining the clinical history of angioedema with or without urticaria, time to onset, and the response to treatment with antihistamines, corticosteroids, and epinephrine. A diagnosis of hereditary or acquired angioedema must be considered if allergic causes and histaminergic mechanisms are unlikely.

Pertinent information in the history includes the following⁵:

1. Characterization of the angioedema
 - Association with/without urticaria
 - Age of onset
 - Time to onset
 - Sites affected (head and neck, peripheries, gastrointestinal tract)
 - Associated symptoms suggestive of an alternative cause or underlying malignancy
2. Response to corticosteroids, antihistamines, and epinephrine
3. Potential triggers or exacerbating factors:
 - Medications (NSAIDs, ACE inhibitors, angiotensin II receptor blockers, narcotics, estrogen-containing oral contraceptives, antibiotics, neuromuscular blocking agents, latex)⁴
 - Dental or surgical manipulation (as they are often triggers of HAE)
 - Stress (mental or physical)
 - Exercise
 - Infections
 - Menses
 - Alcohol
 - Past history of IgE-mediated reactions to foods, medications, insect stings, latex
4. Comorbidities (including autoimmunity and malignancies)

A detailed family history is also essential because HAE-1 and II are of autosomal dominant inheritance; however, up to 25% of all cases may result from spontaneous mutations.³⁴

An Algorithmic Approach to Diagnosis of Angioedema

In encountering a patient with angioedema, one should first establish its association with or without urticaria; if the patient presents with urticaria, histaminergic causes should be explored. Once this differentiation has been made and angioedema mimickers ruled out, this allows for the further classification of angioedema without wheals. If angioedema is unresponsive to antihistamines, corticosteroids, and epinephrine, bradykinin-mediated angioedema should be considered. It is through the appreciation of angioedema subtypes, their respective pathophysiologies, and differentiating features that allows us to apply an algorithmic approach to obtain an accurate diagnosis (Fig. 5).^{47–49} Given the potential severity and life-threatening nature of angioedema, it is essential for medical professionals to reach a prompt diagnosis and initiate the appropriate course of action.

FUTURE CONSIDERATIONS

The accurate diagnosis of angioedema is reliant on a thorough patient and family history, allowing for further stratification through response to treatment, laboratory parameters, and investigations (Table 4).^{18,50–52} Angioedema has been shown to significantly impair one's quality of life,⁵³ affecting both their physical and their mental well-being, and thus establishing a prompt diagnosis, and a treatment plan is

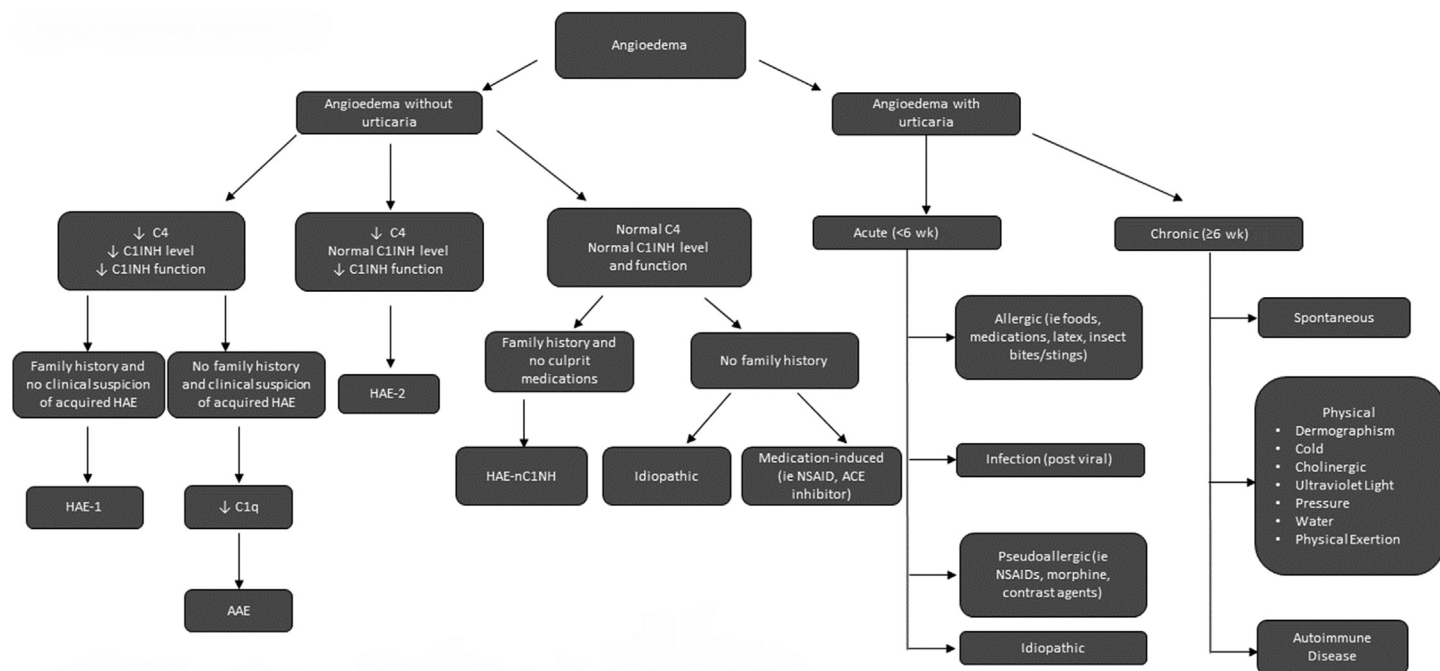


Fig. 5. Angioedema algorithm. AAE, acquired angioedema; C1INH, C1 esterase inhibitor; HAE-nC1NH, hereditary angioedema with normal C1 esterase inhibitor.

Table 4
Summary of the laboratory profiles and evaluation of angioedema

Type	Clinical Description	Antigenetic C1-INH	Functional C1-INH	C1q level	C3	C4	Other Markers
Histamine-mediated							
Allergic angioedema (with urticaria)	- Typically accompanied by urticaria (which may be vasculitic) - Possibly pruritic - May be associated with anaphylaxis 24–72-h duration - Responsive to antihistamines or corticosteroids	NL	NL	NL	NL [‡]	NL [‡]	Urine histamine and serum tryptase often elevated [‡] Complements may be low in hypocomplementemic urticarial vasculitis
Bradykinin-mediated							
Acquired	- Appears in middle age or later - No family history - Unresponsive to antihistamines or corticosteroids - May be associated with an underlying malignancy or autoimmune disorders	Low/NL	Low	Low	Low/NL	Low	A malignancy workup should be considered
ACE inhibitor-induced	- Typically occurs within the first 3 mo of ACE-inhibitor initiation - No urticaria - More common in blacks and smokers - Commonly involves the lips, tongue, face	NL	NL	NL	NL	NL	
HAE-1	- Recurrent episodes of swelling of any body part - Attacks preceded by erythema marginatum in up to ½ of cases - No urticaria - Attacks may last as long as 3–5 d - Symptoms begin in childhood and worsen in puberty - Positive family history - AD inheritance (although up to 25% can occur de novo) - Unresponsive to antihistamines or corticosteroids	Low	Low	NL	NL	Low	

HAE-2	• Same as T1	NL	Low	NL	NL	Low	
HAE-nC1INH	• Same as T1, but may have estrogen sensitivity • Positive family history • Associated with mutations in Factor II • Recurrent tongue swelling is a cardinal symptom • Unresponsive to antihistamines or corticosteroids	NL	NL	NL	NL	NL	
Not conclusively mediated by histamine or bradykinin							
Idiopathic	• ≥ 3 episodes of swelling/y • No apparent cause • Urticaria present in up to 50% • Responsive to antihistamines or corticosteroids	NL	NL	NL	NL	NL	
Pseudo allergic	• Urticaria is typically present • Mechanism is thought to be due to an increase of cysteinyl-leukotrienes (eg, NSAID-induced angioedema)	NL	NL	NL	NL	NL	
Gleich syndrome	• Episodic swelling with eosinophilia and elevated IgM	NL	NL	NL	NL	NL	Elevated IgM antibody, with eosinophilia

Abbreviation: AD, autosomal dominant.

essential. Targeted therapies are under development in the management of both hereditary and acquired forms for the prevention and management of attacks, with the hopes of improving the lives of affected individuals. Research endeavors related to angioedema are aimed at gaining a comprehensive understanding of the pathophysiology and perhaps genetic contributions underlying this disease process to better assist in its evaluation, diagnosis, and management. The establishment of an angioedema registry would aid in the better understanding of the clinical presentation, importance of quality-of-life measures, as well as responses to treatments. It is through a commitment to basic sciences research, clinical trials, and an appreciation for the disease burden that advancements in this field will continue to gain momentum.

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