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CME Review

Isolated angioedema

A review of classification and update on management

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Key Messages

- Hereditary angioedema is very likely if there is a family history of angioedema present and the patient presents in the first or second decade of life. In a subset of patients (25%), the presentation is spontaneous and having a *SERPING1* mutation is required for diagnosis. There are numerous triggers for hereditary angioedema, and fortunately, there are many evolving treatment options that may be disease modifying.
- Acquired angioedema can be distinguished from other types of angioedema based on older age of onset, a low functional and quantitative C1INH level, low C1q, presence of C1 esterase inhibitor antibody, an underlying lymphoproliferative disease, or both.
- Angiotensin-converting enzyme inhibitor (ACEI) angioedema is the most common form of angioedema typically presenting in the emergency department, but laboratory findings such as C4 are normal. Diagnosis is made based on history. Despite discontinuation of the ACEI, recurrent angioedema can occur over weeks to months. Additional therapies reported with various efficacies for treatment of ACEI-induced angioedema include fresh frozen plasma, Ecallantide, Icatibant, tranexamic acid, and C1 inhibitor concentrate. Angiotensin-receptor blockers can safely be prescribed given the low rates of cross-reactivity.
- Histaminergic angioedema can occur by itself or in conjunction with chronic urticaria. The acute form can be allergic, food, or drug related, but often, an underlying cause is not found. Patients often respond well to antihistamines.
- Idiopathic angioedema unresponsive to H_1 antihistamines can be difficult to manage; after a trial of high-dose antihistamines, H_2 antagonists, or a leukotriene receptor antagonist, then a diagnostic and therapeutic trial of oral corticosteroids should be considered. If unresponsive to oral corticosteroids, omalizumab has been reported to be effective. If not effective, then consultation with an angioedema expert is recommended to determine other treatment options before diagnosing as hereditary angioedema normal complement and treating with a hereditary angioedema-approved medication.

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ABSTRACT

Objective: To review the various types of angioedema including diagnosis and treatment.
Data Sources: PubMed search of articles in the English language of various types of angioedema.
Study Selections: Articles on the subject matter were selected and reviewed.
Results: Herein, a case-based approach is presented for discussing the major types of angioedema, including the following: hereditary angioedema types I and II and normal complement, acquired angioedema, angiotensin-converting enzyme–induced angioedema, and histaminergic and nonhistaminergic angioedema. Emerging treatments of hereditary angioedema including targets of prekallikrein, DNA vector technology replacing C1-INH protein, and CRIPSR technology targeting prekallikrein among many others are explored. In addition, other causes and mimickers of angioedema are briefly reviewed. Finally, a novel algorithm is proposed to help guide the treating physician through the workup and management of patients with suspected idiopathic angioedema unresponsive to conventional therapy with antihistamines.

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Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Construct a broad differential and be able to list mimickers of angioedema and angioedema subtypes unresponsive to antihistamines.
- Recognize the clinical presentation and select the best approach to diagnosis and treatment of different types of angioedema.

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Physicians involved in providing patient care in the field of allergy/asthma/immunology.

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Conclusion: Over the years, many strides have been made in both understanding the pathophysiology of various types of angioedema and expansion of treatment options. It is important for clinicians to be aware of current and emerging treatment options. We provide a novel practical algorithm to guide clinicians in challenging cases of idiopathic angioedema refractory to antihistamines.

Introduction

Angioedema (AE) is characterized by swelling that can involve the mucosa, submucosa or subcutaneous tissue of the skin. Usually, AE affects areas with loose connective tissues, including face, lips, mouth, throat, larynx, uvula, extremities, and genitalia,[1] with an asymmetric presentation; AE which affects the bowel wall can mimic an acute abdomen.[2,3] Hippocrates first described swelling of the organs as oídema; however, it was not until the 1800s when Quincke established it as a medical condition after publishing a case series.[4] Since then, numerous clinical observations and scientific advancements resulted in discovery that angioedema can mechanistically involve either bradykinin- or histamine- and leukotriene-mediated pathways. Although C1 esterase inhibitor (C1-INH) deficiency in patients with hereditary angioedema (HAE) is responsible for bradykinin accumulation, histaminergic angioedema is caused by mast cell activation through numerous receptor signaling pathways.[4-6] Today, it is known that AE encompasses a group of conditions with various mechanisms, key distinguishing features, and treatments. Patients with recurrent AE experience a decreased quality of life.[7] Therefore, it is essential that these patients are correctly diagnosed so appropriate therapy is administered. Here, we provide a case-based approach to discuss the presentation and management of various types of AE.

Classification of Angioedema

Overview

The underlying etiology of chronic AE can be divided into the following 2 mechanisms: bradykinin mediated (aka nonhistaminergic angioedema) or histamine mediated (aka histaminergic angioedema).[8] However, a subset of patients do not clearly fit into either designation and they are often referred to as idiopathic nonhistaminergic AE.[9] To complicate matters further, another nonhistaminergic subset of patients referred to as HAE-normal complement present with a family history of AE and normal complement levels. Some of these individuals have been identified to have a specific genetic mutation in pathways that regulate bradykinin production. One key aspect in evaluating AE is determining whether the patient is experiencing urticaria suggestive of histaminergic AE; in contrast, bradykinin-mediated AE is not typically associated with urticaria. Patients presenting with chronic spontaneous urticaria (CSU) have isolated CSU in 40% of cases, CSU with AE in 40% of cases, and isolated AE in up to 20% of cases.[10,11]

When completing an initial assessment for a patient with AE, one should have a broad differential in mind as there are numerous mimickers and miscellaneous causes (Table 1).[12,13]

Miscellaneous etiologies of AE include infections that follow idiopathic AE as the second leading cause of AE in the pediatric population.[14] More recently, viruses such as coronavirus disease 2019 have been known to lead to AE. Supportive care, antihistamines, and treatment of the underlying infection typically lead to resolution. In patients with eosinophilia and AE, the primary consideration is Gleich syndrome characterized by recurrent AE, hypereosinophilia, and often times elevated serum immunoglobulin (Ig)M level; treatment is with oral corticosteroids.[15]

If other conditions are not suspected, then one should evaluate for AE as further outlined in the subsequent sections.

Excess of Bradykinin (Nonhistaminergic)

Pathogenesis

Knowledge of the contact activation pathway is critical for understanding the pathology and therapeutic approaches for bradykinin-mediated AE. The contact activation pathway is initiated when Factor XII (Hageman factor) is activated to form Factor XIIa or if there is prolylcarboxypeptidase-mediated activation of plasma prekallikrein (PKK) to form active plasma kallikrein which cleaves high molecular-weight kininogen to form bradykinin.[16] When bradykinin binds to bradykinin 2 receptors, vasodilation occurs resulting in extravasation of fluid into the interstitial spaces leading to AE. Bradykinin is metabolized by numerous enzymes including angiotensin-converting

Table 1
Mimickers and Miscellaneous Causes of Angioedema

Mimickers	Miscellaneous causes

• Hypothyroidism
• Superior vena cava syndrome
• Contact dermatitis
• Cellulitis
• Autoimmune conditions
  ○ Systemic lupus erythematosus
  ○ Sjögren's syndrome
  ○ Dermatomyositis
• Drug rash with eosinophilia and systemic symptoms
• Morbus Morbihan
• Subcutaneous emphysema
• Orofacial granulomatosis
  ○ Melkersson-Rosenthal syndrome: triad of persisting lip or facial swelling, facial nerve paralysis, and fissured dorsal tongue (lingua plicata)
• Hypocomplementemic urticarial vasculitis syndrome
• Systemic capillary leak syndrome (Clarkson's disease)
• Cluster headache
• Idiopathic edema
	• Infections
	• Drugs and supplements
	  ○ Fibrinolytic agents
	  ○ Calcium channel blockers
	  ○ Herbal supplements
	• Eosinophilic disorders
	  ○ Gleich syndrome

enzyme (ACE), neutral endopeptidase, and aminopeptidase P. C1-INH is critical for regulating the classical (C1r, C1s) and mannan-binding lectin (MASP 1 and 2) pathways, the plasminogen pathway, and the contact pathway to prevent overaccumulation of bradykinin.[17]

Case 1

A 30-year-old woman presents with a history of recurrent swelling of the face, neck, hands, feet, and abdomen with occasional throat swelling sensation. Her symptoms are worse with menses, stress, and after physical trauma such as hitting her hand or medical procedures. She notes a lacy erythematous nonpruritic rash preceding the episodes. Her mother, aunt, and 2 sisters have similar symptoms. Of note, at age 19 years, she had an emergency appendectomy for an acute abdomen and the pathology report noted normal tissue.

Angioedema—Hereditary Angioedema Types I, Type II and Normal Complement

Case Discussion/Clinical Presentation

This patient has AE without urticaria which should always prompt an evaluation for HAE.[18] HAE is an autosomal-dominant disorder that typically presents in the first or second decade of life.[19] Prodromal symptoms are common and include erythema marginatum (as found in our patient), unusual fatigue, and myalgias, which can occur in up to 87% of patients.[20] Erythema marginatum can be difficult to distinguish from urticaria; however, in comparison, it is nonpruritic and faint primarily occurring on the trunk and acral surfaces. The location and severity of the attack can be variable and unpredictable and involve multiple sites.[21] The most common sites involved are the extremities and abdomen; however, up to 50% of patients with HAE will experience a throat swelling episode at some point during their life that may be life threatening owing to asphyxiation.[22] Often, an acute abdominal attack is mistaken for an acute abdomen, which may lead to unnecessary surgical interventions.[23] Additional triggers include ACE inhibitors (ACEIs), estrogen-containing contraceptives, and estrogen hormone replacement—which are all contraindicated in patients with HAE[24] because estrogen can enhance bradykinin signaling. Attacks often begin during puberty (ages 11-13 years old) but have been reported to occur earlier by other investigators (mean age of onset 5.7 years).[25,26] Family history is critical to obtain because 75% have other family members with this disorder. It is important to recognize that 25% of cases are spontaneous mutations without a family history. Therefore, patients presenting with AE without urticaria or a family history should still be screened for HAE.[27,28]

Laboratory Findings

For patients presenting with isolated AE without urticaria, a screening C4 should be obtained, and if low, additional testing should be performed to rule out HAE or acquired angioedema (AAE). Table 2 summarizes the complement laboratory test results in patients presenting with different types of AE. Most patients will have a C4 level that is less than 50% of normal. There are pitfalls with exclusively using C4 to rule out HAE because it can be normal; therefore, if there is high suspicion for HAE, C4 should be repeated during an attack. A low C4 level should prompt testing for C1-INH functional and quantitative levels. There are differences in techniques for C1-INH functional assays leading to differing sensitivities and specificities. The levels of C1-INH antigen and C1-INH functional levels determine which type of HAE the patient may have (ie, type I, type II, HAE normal complement). In patients without a family history of HAE, genetic testing of the *SERPING1* gene is useful for confirming or excluding the diagnosis and differentiating HAE type I and type II from AAE.[29-31]

Management

Patients with HAE do not improve with high-dose H_1 antihistamines or oral corticosteroids; epinephrine only provides transient benefit, but it does not alter the fundamental course of the attack. Treatment of HAE can be administered as acute "on-demand" treatment, short-term prophylaxis (STP), and long-term prophylaxis (LTP). Acute "on-demand" treatment is used to ameliorate symptoms of AE (Table 3A). All patients with HAE should have at least 2 doses of an on-demand therapy in case of acute attacks.[32] On-demand therapy usually works within 1 hour, and requiring a repeat dose within 24 hours indicates worsening of an attack. For abdominal attacks that require a second dose, consideration should be given for other causes of an acute abdomen. Currently approved intravenous C1-INH formulations include plasma-derived nanofiltered C1-INH (Berinert) and recombinant human C1-INH (Ruconest); subcutaneous options are a plasma kallikrein inhibitor (Ecallantide) and a bradykinin receptor antagonist (Icatibant).[33] Plasma-derived C1-INH (pdC1-INH, Cinryze) is approved by the US Food and Drug Administration (FDA) for LTP, but it can be used clinically, if necessary, as on-demand therapy. If these agents are not available, then fresh frozen plasma (FFP) has been used, which was the only on-demand therapy available before 2009; however, there is the potential risk of worsening AE.[32] Decisions on which "on-demand" therapy to use should implement shared decision strategies so patients can determine which treatment is most suitable to their lifestyle and needs. In this case, the patient opted to use icatibant because it was able to be self-injected subcutaneously making it easier to incorporate into her busy schedule.

STP is recommended to protect against a likely attack during a medical procedure (Table 3). STP should be a shared decision process with the patient based on risk of the procedure, cost, and patient preference. If the decision is made not to proceed with STP for lower risk procedures, it is imperative that on-demand therapy be available for the patient. High-risk procedures that can trigger an episode and warrant STP include major dental surgery, intubation, oral surgery, or stressful events.[32] Medications which can be used for STP for HAE type 1 and type 2 include pdC1-INH or recombinant C1-INH treatments as first-line treatments, or if neither of the former are available, anabolic androgens[32,34]; anabolic androgens inhibit bradykinin signaling. Importantly, it has been recommended that the subcutaneous plasma

Table 2
C1-INH and Complement Levels in Angioedema

Angioedema Disorder	C1-INH antigen	C1-INH function	C4	C2	C1q	Autoantibody
HAE type I *85% of cases	↓	↓	↓	↓	Nl	Absent
HAE type II *15% of cases	Nl or ↑	↓	↓	↓	Nl	Absent
HAE with Nl complement (previously known as type III)	Nl	Nl	Nl	Nl	Nl	Absent
AAE	Nl or ↓	↓	↓	↓	↓[a]	Present
ACEI-Induced Angioedema	Nl	Nl	Nl	Nl	Nl	Absent
Idiopathic	Nl	Nl	Nl	Nl	Nl	Absent

Abbreviations: AAE, acquired angioedema; ACEI, angiotensin-converting enzyme inhibitor; C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; Nl, normal level.
[a]C1q has been reported to be normal in some patients with AAE and therefore is not completely reliable as a marker to distinguish HAE and AAE.

Table 3A
FDA-Approved On-Demand Therapeutic Options for HAE[33]

Generic name (trade name, manufacturer)	FDA indications	Dosage	Mechanism	Anticipated potential adverse effects
Plasma-derived nanofiltered C1INH (Cinryze, ViroPharma)	Long-term prophylaxis	1000 U administered intravenously every 3-4 d	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis Theoretical: transmission of infectious agent
Plasma-derived nanofiltered C1INH (Berinert-P, CSL Behring)	Acute attacks	20 U/kg administered intravenously	Inhibits plasma kallikrein, coagulation factors, XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis Theoretical: transmission of infectious agent
Ecallantide (Kalbitor, Dyax)	Acute attacks	30 mg administered subcutaneously (administered as 3 injections of 1 mL each)	Inhibits plasma kallikrein	Uncommon: anti-drug antibodies, risk of anaphylaxis
Icatibant (Firazyr, Shire)	Acute attacks	30 mg administered subcutaneously	Bradykinin B2 receptor antagonist	Common: injection-site reactions
Recombinant human C1INH (Rhucin, Pharming)	Acute attacks (pending)	50-100 U/kg administered intravenously	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Uncommon: risk of anaphylaxis in rabbit-sensitized subjects

Abbreviations: FDA, Food and Drug Administration; HAE, hereditary angioedema; pdC1-INH, plasma-derived C1-INH; rC1-INH, recombinant C1-INH.
NOTE: pdC1-INH and rC1-INH have both been used successfully as short-term prophylaxis.

kallikrein inhibitor and bradykinin 2 receptor antagonist should not be used for STP owing to their short half-life; however, case series have reported that these agents may be effective as well when intravenous C1-INH therapies are not available. This becomes a practicality as many insurance carriers will not approve a second on-demand therapy or the procedure is urgent and there is no time to obtain C1-INH replacement therapy. If patients are already on a subcutaneous or intravenous pdC1-INH or androgens for LTP, then these medications should be dosed around the procedure. Although guidelines recommend STP for all medically traumatic procedures, with the advent of effective LTP therapies (ie, subcutaneous kallikrein and C1-INH therapies), where patients have not had a breakthrough attack, some patients have elected not to use STP before a procedure and have done well.[35] In these circumstances, they should have on-demand therapy on their person and their LTP should be dosed before the procedure. LTP is used to minimize the frequency and severity of attacks. The need for LTP should be shared decision making with the patient and used if necessary to optimize the patient's quality of life.[36] Initiation of LTP depends on frequency, severity, and location of attacks, including availability of on-demand medications, as some insurance carriers limit 3 doses a month. Choice of therapy should be dependent on the patient's age, route of administration, and cost considerations. There are numerous FDA-approved options of various formulations available for LTP, which are summarized in Table 3B.[32]

Emerging treatments of HAE include an *N*-acetyl galactosamine (GalNAc3)–conjugated, second-generation drug targeted to human PKK (Ionis), DNA vector technology replacing C1-INH protein (Biomarin), and CRISPR technology targeting PKK (Intellia), among many other listed in the subsequent texts (Table 4 [37-41]).

Case 2

A 25-year-old woman presents with recurrent facial AE every 2 to 3 weeks with minimal responsiveness to oral corticosteroids, cetirizine 20 mg twice a day, famotidine 20 mg once a day, and montelukast 10 mg once a day. Numerous family members have AE including 3 first cousins, an uncle, and a grandmother. Results of laboratory values including C4, C1-INH antigen, and C1-INH function are all normal.

Case Discussion

This patient has HAE normal complement which is challenging to diagnose, differentiate, and manage. Distinguishing clinical features of HAE normal complement from HAE type 1 or type 2 beyond normal laboratory values include are that it affects predominately individuals of female sex, is more reactive to estrogens and responsive to progesterone, is associated with a higher incidence of facial attacks, and has an older age of onset.[42,43] In contrast to nonhistaminergic idiopathic AE, often family members are affected although in lower instances than in HAE. Genetic mutations associated with HAE normal complement include a Factor XII enzyme mutation and more rarely with other mutations, including angiopoietin-1, plasminogen, kininogen, myoferlin, and heparin sulfate.[32,44] In the setting of normal laboratory values as discussed previously, the diagnosis of C1-INH with normal complement hinges on either a family history or presence of the genetic mutations listed previously. Overall, treatment of HAE normal complement follows similar principles as treatment of type 1 and type 2 HAEs with importance of prescribing on-demand and STP therapies. Owing to the rarity of HAE normal complement, there are fewer studies addressing therapy, thus adding to the difficulty in managing these patients. Tranexamic acid, progesterone, androgens, and C1-INHs were all found to be efficacious.[24,32,45] The patient in case 2 was placed on tranexamic acid (TXA) for LTP and had icatibant available for on-demand therapy. She was instructed to notify her physician if she decided to have children, at which point, the TXA would be changed to an alternative therapy, such as a kallikrein inhibitor or pdC1-INH replacement therapy.

Case 3

A 69-year-old woman presents with recurrent lip and tongue edema occurring weekly. She has no identifiable triggers, no family history, and is not taking an ACEI. A screening serum C4 level (8 mg/dL; nl 16-48 mg/dL) was low prompting further workup which revealed low C1-INH quantitative (9 mg/mL; nl 19-37 mg/dL), functional (<40%), and C1q (6 mg/dL; nl 12-22 mg/dL) levels. Additional testing included a serum protein electrophoresis which revealed an M spike. Follow-up testing result revealed that the patient had increased IgG antibody to C1-INH.

Acquired Angioedema

Case Discussion

AAE is a rare form of AE and typically affects older individuals (>40 years of age). It presents as an overactivation of the classical complement pathway resulting in consumption of C1-INH either secondary to an underlying lymphoproliferative disorder or because of formation of a C1-INH autoantibody that neutralizes C1-INH function.[46] The most common lymphoproliferative disorders include monoclonal gammopathy of uncertain significance and Hodgkin's

Table 3B
FDA-Approved Long-Term Prophylaxis Options for HAE

Name	Mechanism	Route	Age approval	Dose (manufacturer label) and adverse effects
FDA-approved options				
Cinryze	pdC1-INH	Intravenous	6 y and older	Pediatric dosing 6-11 y: 500 U intravenous every 3-4 d (can be adjusted up to 1000 U) Adults and teenagers 12 y and older: 1000 U intravenous every 3-4 d (can be adjusted at 1000 U doses up to 2500 U not exceeding 100 U/kg) Serious reactions: hypersensitivity reactions/anaphylaxis, thromboembolism, theoretical viral transmission Common AE symptoms: headache, nausea, vomiting, nasopharyngitis, rash, catheter site pain, dizziness, erythema, pruritus.
Haegarda	Pd-nanofiltered C1-INH	Subcutaneous	6 y and older	≥ 6 y (including adolescents and adults): Subcutaneous: 60 U/kg/dose every 3 or 4 d Adverse effects same as Cinryze
Lanadelumab (Takhzyro)	Monoclonal antibody that inhibits plasma kallikrein	Subcutaneous	12 y and older	12 y and older: 300 mg administered subcutaneously every 2 wk (if patient is well controlled can consider a dosing interval of 300 mg every 4 wk) Adverse reactions: hypersensitivity reaction, injection site reaction, rash, myalgia, dizziness, liver function test elevation
Berotralstat (Orladeyo)	Synthetic small molecule that inhibits plasma kallikrein	Orally	12 y and older	12 y and older: 150 mg once daily Adverse reactions: abdominal pain, vomiting, diarrhea, headache, fatigue, flatulence, back pain, GERD.
Androgens (Danazol)	Attenuated androgen	Orally		Adolescents aged more than or equal to 16 y: Initial: 2.5 mg/kg/d; maximum initial daily dose: 50 mg/d; increase slowly every 2 wk until symptoms controlled or maximum tolerated or maximum recommended dose is reached; maximum daily dose: 5 mg/kg/d up to 200 mg/d. Adults: 100-200 mg once daily. Serious reactions: hepatic impairment, thromboembolism, contraceptive failure, virilization, hepatic adenoma, pseudotumor cerebri Common adverse reactions: acne, vaginitis, menstrual irregularities, weight gain, emotional lability, hirsutism, deepened voice, hepatic impairment, spermatogenesis
Non–FDA-approved for HAE indication but guideline-recommended options				Reported doses
Tranexamic acid	Inhibits plasmin formation	Orally	N/A	Pediatric[31]: 20 mg/kg orally twice a day (10 mg/kg twice a day to 25 mg/kg thrice a day) Adult[31]: 1 g orally twice a day (0.25 g twice a day to 1.5 g thrice a day) Pediatric: 20 mg/kg orally twice a day (10 mg/kg twice a day to 25 mg/kg thrice a day) Serious reactions: hypersensitivity reactions, anaphylaxis, thromboembolism, retinal venous occlusion, cerebral edema or infarction, seizures, ureteral obstruction Common adverse reactions: headache, URI symptoms, back pain, abdominal pain, musculoskeletal pain, arthralgia, muscle cramps, migraine, anemia, nausea, fatigue, vomiting, diarrhea, dizziness, vision changes, allergic contact dermatitis (intravenous use only) and hypotension (intravenous use only)
Progesterone[a] (Females)	Orally most studied Various methods available (patch, ring, etc.)	Orally	N/A	No established dosing. Some report starting at norethindrone 0.35/d[31]

Abbreviations: AE, angioedema; C1-INH, C1 esterase inhibitor; FDA, Food and Drug Administration; GERD, gastroesophageal reflux disease; HAE, hereditary angioedema; N/A, not available; pdC1-INH, plasma-derived C1-INH; URI, upper respiratory tract infection.
[a]Can consider first line for females for HAE with normal complement.[36]

Table 4
Emerging and Novel Treatments of HAE

Emerging treatment	Description
IONIS-PKKRx	Antisense inhibitor of PKK and bradykinin production: binds and selectively reduces *PKK* mRNA in the liver.[37] Well tolerated in phase 1 studies.[37]
BMN 331 (Biomarin)	Preclinical. Goal of introducing *SERPING1* gene into the body using DNA vector technology enabling patients to produce their own functional C1-INH protein[38]
NTLA-2002 (Intellia)	Single-dose therapy development; uses in vivo CRISPR or Cas9 genome editing/currently in phase 1/2 of clinical trial in Australia. Designed to inactivate the target gene *KLKB1* to reduce plasma kallikrein activity.[39]
Garadacimab	Fully human, IgG4 monoclonal antibody which targets activated FXII for patients with HAE.[40] Currently in phase 3.
KVD824	Oral small molecule inhibitor of PKK. Recruiting for phase 2.
ALN-F12	Subcutaneously administered GalNAc-conjugated siRNA targeting F12 mRNA (ALN-F12) and decreases vascular permeability.[41]
PHA-022121	Small molecule bradykinin 2 receptor antagonist (oral). Recruiting for phase 2.

Abbreviations: HAE, hereditary angioedema; IgG4, immunoglobulin G4; mRNA, messenger RNA; PKK, prekallikrein; siRNA, small-interfering RNA.

lymphoma.[47,48] Type 1 and type II nomenclature is no longer used because many patients have an overlapping lymphoproliferative disorder with C1-INH autoantibody. The laboratory evaluation for AAE is similar to HAE and should include serum C4, C1-INH quantitative, functional, and C1q levels. In addition, a C1-INH antibody and serum protein electrophoresis with reflex immunofixation should be obtained to rule out the presence of a lymphoproliferative disorder. Compared with other types of AE, C1q is low 70% to 80% of the time and C1-INH antibody may be positive.[46] If evidence of a lymphoproliferative disease is found, consultation with a hematology and oncology specialist is recommended. Icatibant has been used successfully as an on-demand therapy for AAE; variable responses have been reported for pdC1-INH or rC1-INH especially in patients with a C1-INH autoantibody, which may neutralize the C1-INH treatment or act as a substrate for producing more antibody.[49] Currently, there are no approved LTP agents for AAE and no consensus on treatment. Androgens and TXA have both been reported to be effective treatments; agents that target B cell clones such as rituximab and cyclophosphamide have been reported with variable success.[46,50] There are now multiple studies that suggest TXA is a safe and effective treatment of AAE albeit providers should counsel on potential adverse effects, including thrombotic evens and hypersensitivity reactions. However, there is still a need to investigate whether novel safe therapies for HAE are also effective for the treatment of patients with AAE.[49-51]

Case 4

A 46-year-old woman presents to the emergency department with AE of the lips and tongue which presented when she awoke. The swelling was treated with H_1-antihistamines and intravenous corticosteroids without benefit. Because the swelling involved the tongue and was not subsiding, she was admitted into the intensive care unit for ongoing observation and airway protection if needed. Fortunately, after 12 hours, the swelling started to subside and completely resolved after 24 hours. She has had 2 other episodes in the past 3 to 4 weeks which were milder and resolved on their own after 2 to 3 hours without medication. She has no associated urticaria, and there were no known triggers related to the swelling onset. She has been taking lisinopril 10 mg once a day for the past 6 months. Her laboratory findings included a normal complete blood cell count with differential, complete metabolic profile, and serum C4 level.

Angiotensin-Converting Enzyme–Induced Angioedema (Angioedema-Drug Induced)

Case Discussion

This patient has ACEI-induced AE. ACE also known as kinase II not only acts on the renin-angiotensin system but is also important for degradation of bradykinin. Therefore, it is thought the most likely explanation for ACEI AE is through excess bradykinin but other pathways are likely involved that result in defective breakdown of other vasodilatory products, such as substance P.[52] Because ACEIs are frequently prescribed antihypertensives in the United States, it is not surprising that ACEI AE accounts for one-third of the patients who present to the emergency department for AE.[53,54] Diagnosis is based on history, and if obtained, laboratory findings such as C4 and other complement levels are normal (Table 2). Clinical presentation is classically associated with facial and oral cavity swelling whereas visceral manifestations are uncommon.[55,56] AE can still occur at any point during ACEI therapy although a large study reported that more than half (66%) occurs within the first 3 months after initiation.[57]

Risk Factors

Numerous studies have reported that Black, female sex, patients aged more than 65 years old, and patients taking nonsteroidal anti-inflammatory drugs are at increased risk for ACEI AE.[58-61] It is important to recognize that other medications such as gliptins, which are dipeptidyl peptidase 4 inhibitors, are also associated with increased risk of AE.[62,63] Other identified risk factors for more serious outcomes such as intubations include smoking, calcium channel blocker use, and age.[64]

Management

The recommended treatment of ACEI is discontinuation of the medication. It is important to keep in mind that despite discontinuation of the ACEI, recurrent AE can occur for several weeks to months; in 1 long-term study, 46% of patients had recurrence of their AE symptoms mostly within the first month.[65] Initial medical management should focus on securing an airway if swelling involves the oropharynx. The Ishoo Classification for AE is one rating scale that has been used by clinicians to evaluate whether patients can be safely discharged home or should be admitted to the hospital or intensive care unit for observation in case intubation is required.[66] Life-threatening and fatal cases of ACEI AE have been reported.[67] Given the involvement of the bradykinin pathway, it is not surprising that antihistamines and corticosteroids are minimally effective.[68,69] Although epinephrine is not effective for the AE, it can be used in the management of patients with respiratory distress secondary to the severity of their AE.[69] There are currently no FDA-approved medications for ACEI AE; however, several therapies have been reported to be effective with variable efficacy, including FFP (contains kininase II), ecallantide (direct inhibitor of plasma kallikrein), icatibant, TXA, and C1 inhibitor concentrate. Of note, FFP has the potential to worsen AE and, therefore, should be used with caution. In addition, bradykinin 2 receptor antagonists are first line for ACEI AE in France but potentially have limited efficacy in Black patients.[70]

It is important to note that there are low rates of cross-reactivity between ACE and angiotensin-receptor blockers (ARBs) because ARBs do not work through the bradykinin pathway.[71] However, there are a few case reports of patients with ACEI AE who developed AE after switching to an ARB. It is unclear whether the AE was a continuation of AE induced by the ACEI as previously described or a new

event caused by the ARB.[71] Therefore, although ARBs are typically tolerated, caution should be exercised in switching these patients to an ARB unless medically necessary.

Idiopathic Angioedema

Case 5

A 65-year-old woman presents with recurrent lip swelling without urticaria twice a month in the past year. She is not currently taking an ACEI, nonsteroidal anti-inflammatory drug, or other medication associated with AE. Her symptoms respond partially to diphenhydramine, which causes sedation, but are completely resolved with oral corticosteroids. She has been prescribed courses of corticosteroids monthly for these swelling episodes in the past year.

Case Discussion and Overview

This patient has chronic recurrent AE without urticaria partially responsive to H_1-antihistamines but has never been started on daily prophylactic H_1-antihistamines or had dose escalation to 2 to 4 times the FDA-approved doses of H_1-antihistamines as recommended for CSU. Typically, these patients are referred to as "idiopathic histaminergic AE,"[72] which is the most common form of AE and should be managed similarly to CSU.[73] Histaminergic AE can be differentiated from nonhistaminergic AE by its more rapid onset of symptoms, shorter duration (resolves in 24-48 hours), and response to H_1-antihistamines and oral corticosteroids.[73] Histaminergic AE can be classified as being acute (≤6 weeks) vs chronic (>6 weeks) and further categorized by presence or absence of urticaria. It is important to understand that although histamine is involved with each AE subtype primarily owing to the activation of mast cells, there are various mechanisms for mast cell activation other than IgE receptor cross-linking as illustrated in Figure 1.[74]

Allergic AE is a subtype of histaminergic AE which most often presents with acute urticaria triggered by an inciting allergen, such as foods, venoms, and drugs. This presentation can often be difficult to distinguish from anaphylaxis because patients may experience throat tightness or shortness of breath owing to anxiety. The criteria for anaphylaxis have been reviewed by many professional organizations which differ in their definitions, making it challenging for the treating physician to differentiate from acute urticaria with AE.[75,76] Although antihistamines are effective in management of isolated allergic AE, it is important to err on the side of caution and treat with epinephrine as first-line treatment until appropriate referral to an AE expert can be made to differentiate between these conditions.

Chronic AE with urticaria has been better described with clearer management recommendations in comparison to chronic AE without wheals. There are 2 major CSU guidelines: The US Joint Task Force Urticaria Guideline last updated in 2014 and the international guidelines, which is a Grading of Recommendations, Assessment, Development and Evaluation guideline, last updated in 2021.[8,77,78] Comparison of the similarities or differences between these guidelines has previously been reviewed.[79] The presence of AE has been associated with a more severe form of CSU, but studies have found that many of these patients may have a favorable response to omalizumab if unresponsive to antihistamines.[80,81]

Given the various management guidelines of CSU and allergic AE which both lead to AE with urticaria, our discussion in this review will primarily focus on chronic AE without wheals because there is a less clear consensus on managing these patients.

Chronic Angioedema Without Wheals

In general, chronic AE without wheals requires a workup to rule out additional etiologies including a C4 level although a normal C4 level does not rule out HAE normal complement. Although 1 study from a large referral center reported that approximately one-third of their patients had idiopathic histaminergic AE, the epidemiology of

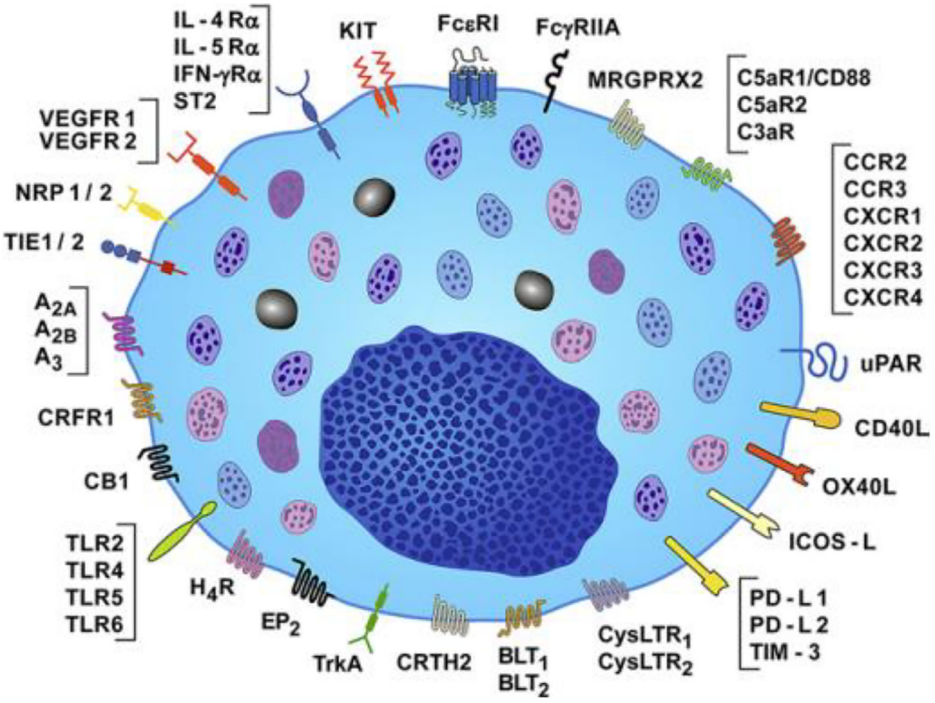

Figure 1. Various mechanisms of mast cell activation. Mast cells, which express numerous surface receptors, including FcER1, FcγR, ckit, hormonal, complement, opioid, cytokine, chemokine, and TLR, can be activated by relevant ligands (not illustrated are inhibitory receptors such as Siglec 8 and 9). Additional triggers include medications (nonsteroidal anti-inflammatory drugs, opioids) or pathogens.[75] FcεR1, high-affinity IgE receptor; FcγR, Fc gamma receptor; IL-4 or -5, interleukin-4 or -5; TLR, toll-like receptor; VEGFR, vascular endothelial growth factor receptor.

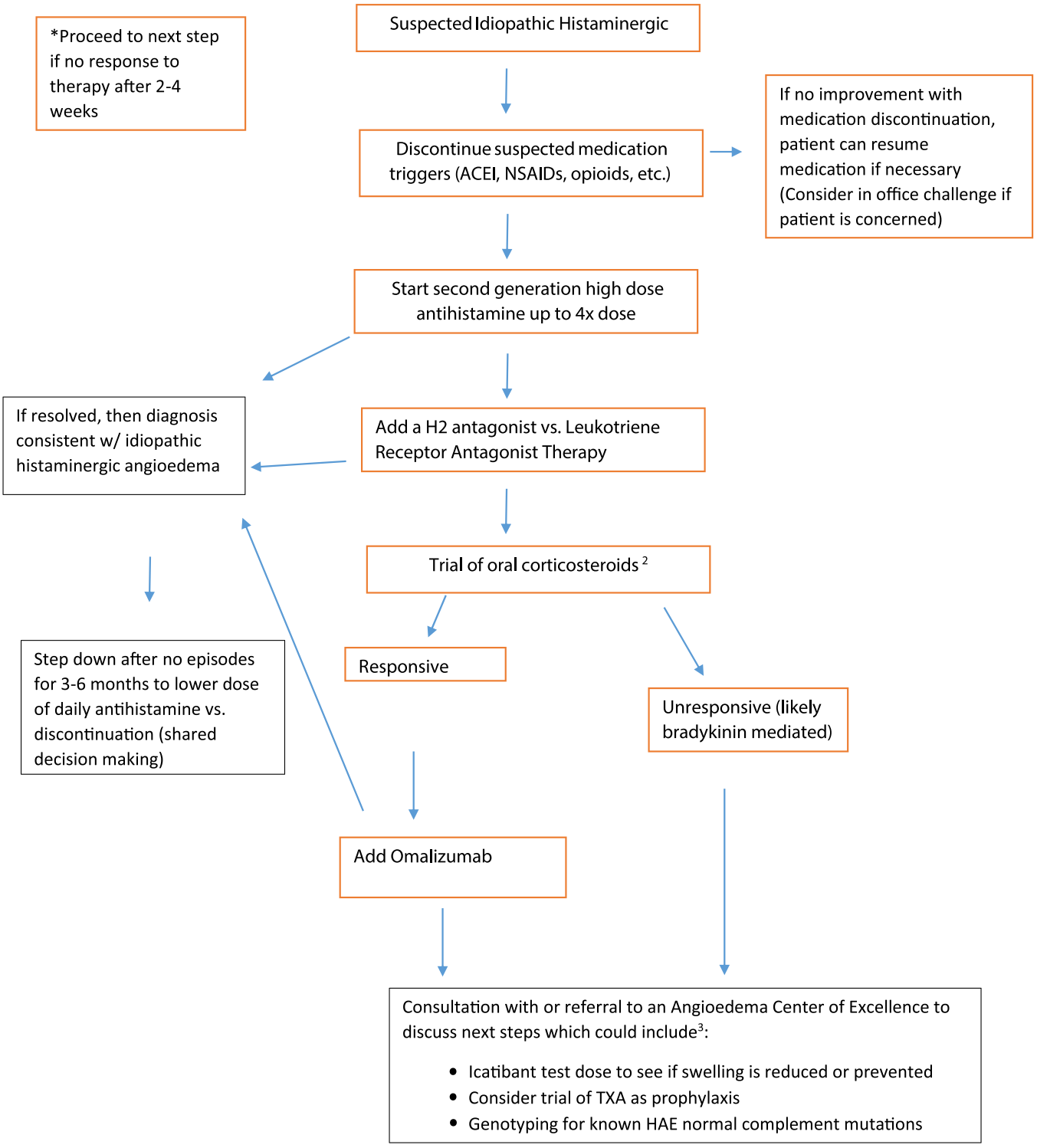

Figure 2. Management of idiopathic angioedema without urticaria. [1]Diagnose after excluding other causes (HAE, drug induced, etc.). [2]More than 12 years old, prednisone 35 to 40 mg for 5 to 7 days and if tapering reduce 5 mg every 2 days until off. Less than or equal to 12 years old, consider 0.5 mg/kg for 5 to 7 days and increase if clinically necessary. [3]Angioedema Center of Excellence: acare-network.com. ACEI, angiotensin-converting enzyme inhibitor; HAE, hereditary angioedema; NSAID, nonsteroidal anti-inflammatory drug; TXA, tranexamic acid.

this condition remains limited.[82] Most of these patients seem to respond to high-dose antihistamines[82]; however, there is no clear consensus on how to treat these patients if they are unresponsive to H_1-antihistamines. Figure 2 is a proposed algorithm for the treatment of such patients. There is general consensus that histaminergic AE should be at least partially responsive to high-dose H_1-antihistamines. Although we agree with this recommendation, some patients with histaminergic AE may also be responsive to the addition of a leukotriene receptor antagonist, H_2 antihistamine or both.[83] Although scientific evidence supporting the use of these later 2 agents is low, they are inexpensive and generally well tolerated, and subsets of patients respond clinically.[83] Furthermore, histaminergic angioedema is typically responsive to oral corticosteroids which may be a good diagnostic therapeutic way to differentiate this condition from nonhistaminergic

angioedema. If responsive, we suggest following the CSU protocol for management.[84]

If unresponsive to the above-mentioned therapies, these patients are often classified as having idiopathic nonhistaminergic AE. Unfortunately, many of these patients are subsequently treated with HAE medications inappropriately or prematurely which is extremely costly and often not effective. Because there are nuances in the evaluation and treatment of idiopathic nonhistaminergic AE, it is recommended these complex cases be referred to an experienced AE specialist or if not practical, the treating physician should consult with an AE expert to discuss further evaluation and management recommendations. In many instances, these patients have been treated successfully with other therapies including the CSU step 3 and step 4 therapies omalizumab[85] and cyclosporine, respectively, or TXA suggesting the involvement of other non–bradykinin-mediated pathways.[72,86,87] If a diagnosis of HAE normal complement is being considered, some clinicians have used icatibant diagnostically and therapeutically to evaluate whether these patients have HAE normal complement; however, it can sometimes be difficult to assess its clinical effectiveness. A recent retrospective report emphasizes the clinical heterogeneity and variability of response to icatibant necessitating the need for biomarkers that can distinguish between histaminergic and nonhistaminergic angioedema and improve the value of using icatibant in patients with nonhereditary angioedema.[88] Because genetic mutations in these patients are rare and often not present and there are no other commercially available diagnostic biomarkers, diagnosis of HAE normal complement remains very challenging to diagnose further emphasizing the need to discuss these cases with experts when the above-mentioned non-HAE therapies prove ineffective.

Conclusion

AE is a heterogeneous condition which allergists and immunologists most often encounter in their clinical practice and, therefore, should be comfortable in diagnosing and managing. In this review, we have provided an overview of AE without urticaria including discussion of emerging insights and treatment options. Clinicians must stay up to date on management to provide the best treatment options for their patients to control this condition and improve their patient's quality of life. Some of the above-mentioned cases discussed can be very complicated to diagnose (eg, C1-INH HAE normal complement or nonhistaminergic angioedema) owing to lack of diagnostic biomarkers and to treat given our poor understanding of their pathomechanisms. It is recommended that clinicians managing these cases have an open forum with AE experts to discuss these cases in greater detail and collectively decide on best treatment options before empirically starting costly and often ineffective therapies. Future treatments for HAE include antisense PKK inhibitors, Factor XII antagonists, genetic therapy to replace C1-INH or inactivate PKK, and oral kallikrein or bradykinin antagonists for on-demand or prophylactic use. Therapies for histaminergic angioedema unresponsive to H_1-antihistamines are lacking. Thus, further investigations of current or novel therapies designed to treat urticaria should be repurposed for investigation of isolated histaminergic angioedema. Similarly, treatment is lacking for HAE normal complement and other forms of nonhistaminergic angioedema emphasizing the need to better understand the pathogenesis of these conditions.

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