Clinical presentation, pathophysiology, diagnosis, and treatment of acquired and hereditary angioedema: Exploring state-of-the-art therapies in RI

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ABSTRACT

Hereditary and acquired angioedema are potentially life-threatening diseases characterized by spontaneous episodes of subcutaneous and submucosal swelling of face, lips, oral cavity, larynx, and GI tract. Hereditary angioedema (HAE) usually presents within the first and second decades of life, whereas acquired angioedema presents in adults after 40 years of age. These clinical symptoms together with reduced C1 inhibitor levels and/or activity can usually confirm the diagnosis. In recent years, multiple novel therapies for treating hereditary angioedema have emerged including C1 inhibitor concentrates, ecallantide/kallikrein inhibitor, and icatibant/bradykinin receptor antagonist. This article reviews the clinical presentation, diagnosis, treatment, and prophylaxis of HAE. Lastly, this article takes into consideration that, in reality, acute care treatment can often be limited by each hospital's formulary, included is a review of HAE treatments available at the nine major hospitals in Rhode Island.

KEYWORDS: hereditary angioedema, acquired angioedema, Rhode Island, C1-INH

INTRODUCTION

Hereditary and acquired angioedema are conditions characterized by acute swelling of the subcutaneous and submucosal tissues, which can progress to involve more surface areas or threaten life when it involves the laryngeal tissue. In addition to causing significant mortality and morbidity, HAE attacks are also associated with significant loss of school/work days and reduction in quality of life. Hereditary angioedema (HAE) is an autosomal dominant condition which occurs in about 1:10,000 to 1:50,000 in the general population [1]. Acquired angioedema (AAE) occurs in about 1:100,000 to 1:500,000 in the general population [2]. Given that the population of Rhode Island (RI) is estimated to be about 1 million people [3], this extrapolates to a prevalence of 20–100 patients with HAE and 2–10 patients with AAE in RI.

Fortunately, novel targeted therapies for acute HAE exacerbations have emerged in the last 7 years. This article reviews the clinical presentation, diagnosis, prophylaxis and treatment of attacks. Also included is a review of currently available HAE treatments at the nine major hospitals in RI because, in reality, acute care treatment in the emergency department (ED) is often limited by a local hospital's formulary.

This is a qualitative and not a systematic review of the treatment of HAE, and by extension, AAE.

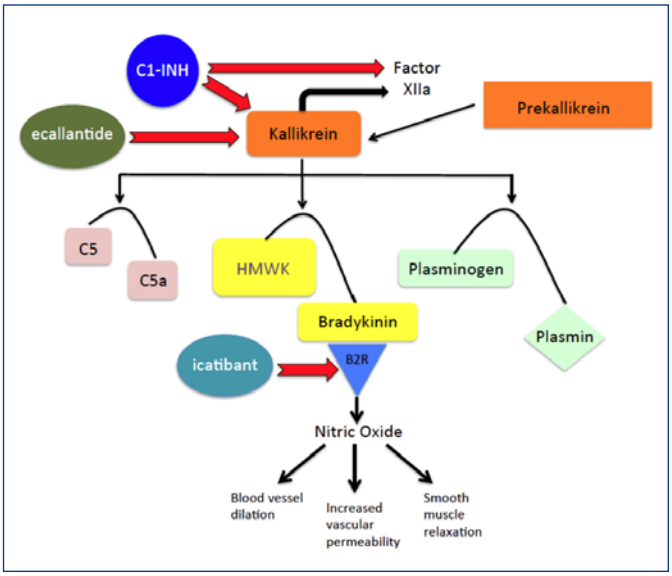
CLINICAL PRESENTATION

Patients with HAE and AAE experience recurrent episodes of submucosal and subcutaneous edema involving the face, tongue, GI tract, or larynx, which may be life threatening. The severity and frequency of acute attacks of angioedema are variable, ranging from once/year to three attacks/week [4]. HAE usually first clinically presents in the 1st and 2nd decades of life, whereas AAE usually presents after 40 years of age [2]. AAE is frequently due to an underlying lymphoproliferative or autoimmune disorder [5].

PATHOPHYSIOLOGY

The underlying pathophysiology of angioedema involves the activation of the kallikrein-kinin cascade. C1-INH directly inhibits both kallikrein and Factor XIIa, the latter of which catalyzes the formation of kallikrein (**Figure 1**). Once formed, kallikrein converts high molecular weight kininogen (HMWK) into bradykinin, which activates its receptor B2R

Figure 1. Kallikrein-kinin cascade and targeted therapeutic interventions.



to stimulate nitric oxide release, blood vessel dilation, and increased vascular permeability, resulting in angioedema.

DIAGNOSIS

Although this article focuses on HAE and AAE, it is important to appreciate that these diseases are amongst the least common causes of angioedema that present to the ED. Angioedema accounts for about 100,000 visits to the ED each year [6]. The most common cause of angioedema (severe enough to warrant an ED visit) is ACE-inhibitor induced angioedema, accounting for 20-40% of ED presentations [7, 8]. Another common culprit for angioedema is nonsteroidal anti-inflammatory drug (NSAID)-induced angioedema accounting for 11% of cases [9, 10]. Often, however, the cause is never identified; these idiopathic cases are referred to and further subdivided into histaminergic and nonhistaminergic variants.

There are three types of HAE. Type I is characterized by a quantitative decrease in C1-INH level (majority of cases); Type II, by a reduction in functional C1-INH activity; and Type III, by normal C1-INH level and activity (rare). Type III patients are almost exclusively female and have a positive family history or Factor XII mutation or defects in bradykinin metabolism (**Table 1**).

Diagnosis may be made in the appropriate clinical setting by obtaining two separate serologic measurements demonstrating decreased C4 levels and C1-INH antigen or function 1-3 months apart [2]. Decreased C4 levels and C1-INH antigen or function also characterize AAE. Measurement of C1q is useful to distinguish HAE from AAE; it is normal in HAE, but low in AAE [11]. There are two types of AAE. Type I occurs when immune complexes consume C1-INH; Type II, when anti-C1-INH antibody neutralizes C1-INH (**Table 1**) [12].

HAE has been associated with mutations in the SERPING1 gene [2]. Genetic testing should be considered when clinical and laboratory data are insufficient for diagnosis. Patients diagnosed with AAE should undergo work-up for underlying lymphoproliferative and autoimmune disease [5, 11].

Table 1. Differentiating laboratory findings in acquired angioedema and hereditary angioedema. Red arrows indicate decreased level or function; blue arrows indicated increased level or function.

		C1-INH level	C1-INH activity	C1q	C4	C1-INH Ab
HAE	Type I	↓	↓	normal	↓	none
	Type II	normal or ↑	↓	normal	↓	none
	Type III	normal	normal	normal	normal	none
AAE	Type I	↓	↓	↓	↓	none
	Type II	normal or ↓	↓	↓	↓	↑

TREATMENT OF ACUTE ATTACKS

The recommendation from the international allergy/immunology and emergency medicine community is to treat acute attacks of hereditary angioedema because the consensus is that treating acute attacks will reduce mortality [2, 13-15]. Though the literature lacks a study that randomizes patients to treatment or placebo to specifically examine mortality – a study unlikely to be approved by an IRB – there is a study that examined 70 patients of whom asphyxiated from a laryngeal attack, 63 (90%) of those were undiagnosed [16]. Undiagnosed patients often receive inappropriate therapy (including surgery) or delay in emergency treatment [16-18]. Lastly, there's no evidence that treating acute attacks of hereditary angioedema increases mortality. Given the efficacy, safety profile, and risk of withholding treatment, the international allergy/immunology and emergency medicine community recommends administering therapies during an acute attack [2, 13-15].

The major goals of treating acute attacks are to avoid asphyxiation and provide symptomatic relief. Mechanistically, treatments should halt or dampen activation of kallikrein-kinin cascade (**Figure 1**). Therapies target crucial points in the pathway. C1-INH is a serine protease that directly inhibits kallikrein and factor XIIa. Two brands of C1-INH are currently FDA approved for acute attacks of HAE; Berinert® (CSL Behring, King of Prussia, PA) is the human plasma derived C1-INH and Ruconest® (Salix, Raleigh, NC) is a recombinant C1-INH derived from New Zealand white rabbit oocytes. Other FDA-approved treatments for acute attacks include the kallikren inhibitor, ecallantide/Kalbitor® (Dyax, Burlington, MA) and bradykinin receptor antagonist, icatibant/Firazyr® (Shire, Lexington, MA).

Currently there are no FDA-approved therapies for AAE. Management of AAE focuses on treating the underlying condition. Additionally, it is commonplace in medical practice to make off-label use of the above HAE products for the treatment of acute AAE attacks. However the evidence for this utilization is limited to case reports [19, 20].

In clinical practice, acute care treatment in the ED is often limited by local hospital formulary. In Rhode Island, of the nine major hospitals with emergency departments, only five carry treatment for acute HAE attacks on their formularies at the current time (**Table 2**). This information is important to consider when referring HAE/AAE patients for ED care.

Berinert®

Ten studies have been performed, involving 537 subjects. One randomized controlled trial showed that treated subjects had a statistically significant benefit in time to relief and time to complete resolution, as compared with placebo treatment, and with a lower adverse event profile. Currently Berinert is FDA approved for on demand self-administration of acute attacks and can be administered at home or in the ED.

Table 2. HAE acute treatment availability per local hospital formularies in Rhode Island as of March 10th, 2016.

Hospital	Medication on formulary
Rhode Island Hospital	Berinert
The Miriam Hospital	Berinert
Newport Hospital	Berinert
South County Hospital	Berinert
Westerly Hospital	Kalbitor
Kent Hospital	None
Roger Williams Medical Center	None
Memorial Hospital	None
Landmark Medical Center	None

Ruconest®

Two randomized, placebo controlled trials (RCTs), showed that the median time to start of symptom relief was significantly lower in the Ruconest arm at 100 U/kg (66 vs 495 minutes, *p-value* <0.001), and at 50 U/kg (122 vs 495 minutes, *p-value* 0.013) [22].

An assessment for IgE mediated hypersensitivity to rabbit can be performed prior to administration in patients with suspected rabbit allergy. Appropriately trained patients may self-administer upon recognition of an HAE attack. As such it can be administered at home or in the ED.

Ecallantide/Kalbitor®

Ecallantide is a direct kallikrein inhibitor. The EDEMA 3 and 4 were RCTs designed to evaluate efficacy and safety of ecallantide [23, 24]. EDEMA3 found significantly greater symptom relief compared to placebo (p-value 0.004) [23]. EDEMA4 showed significant improvement of symptoms compared to placebo at 4 hours (*p-value* 0.01) and at 24 hours (*p-value* 0.04) [24]. Adverse events were mildly increased in the treatment arms [23, 24].

It is not approved for self-administration at home because 3% of patients experienced anaphylaxis [1]. In order to heighten awareness of this anaphylaxis risk, the FDA has required that the prescribing information include a black-box warning mandating that only health-care professionals trained in managing anaphylaxis administer this drug. In order to facilitate treatment in patients who may be traveling, the manufacturer has a program, which coordinates the services of a healthcare professional to administer the medication at a medical facility in close proximity to the travel destination.

Icatibant/ Firazyr®

Icatibant (Firazyr) acts through an alternative mechanism to interrupt the kallikrein-kinin pathway by blocking the bradykinin receptor (**Figure 1**). While one RCT failed to show a reduction in time to improvement, another demonstrated that the median time to symptomatic reduction of 50% or more in moderate to very severe acute episodes was achieved in a significantly shorter time in the icatibant group than placebo group (2 vs 19.8 hours, *p-value* <0.001) [26]. Time to complete relief of symptoms was also significant (8.0 vs 36.0 hours, *p-value* <0.001) [26]. Icatibant is FDA approved for subcutaneous self-administration of acute attacks of hereditary angioedema and can be administered in the ED or home setting.

Each of these drugs has FDA approval for treatment during acute attacks. Because there are no trials comparing these therapies to each other, it is left to the medical care professionals to determine the most efficacious and safest treatment option for acute care of each patient. The therapies are summarized in **Table 3**.

Table 3. Comparing and contrasting FDA-approved therapies for acute HAE attacks with respect to relative advantages, mechanism of action, route of administration, half-life, adverse events, and approved indication. *Adverse events occurring at frequency greater than 2% documented in the prescribing information [39-42].

Drug	Advantages	Mechanism of Action	Route of Administration	Half-life (hours)	Adverse Events*	FDA Approval
Berinert®	Long half-life, more likely to avoid re-dose	Replacement with plasma derived C1-INH	IV	22.4 in children, 16.7 in adults	Nausea, dysgeusia, abdominal pain, vomiting	Self-administration in adolescents and adults
Ruconest®	No known risk of human viral transmission	Replacement with recombinant rabbit oocyte derived C1-INH	IV	2.5	Headache, angioedema, vertigo	Self-administration in adolescents and adults
Ecallantide/ Kalbitor®	Subcutaneous administration	Recombinant plasma kallikrein inhibitor	SQ	2	Headache, nausea, diarrhea, pyrexia, injection site reaction, nasopharyngitis	Trained healthcare professional administration for patients >12 years old
Icatibant/Firazyr®	Subcutaneous self-administration.	Bradykinin receptor antagonist	SQ	1.4	Injection site reaction, pyrexia, dizziness, transaminase increase	Self-administration in those >18 years old

PREVENTION

HAE and AAE patients who suffer particularly severe or frequent attacks may receive long-term prophylaxis. It may also be reasonable to administer a short course of prophylaxis prior to dental procedures, surgeries or other events likely to precipitate an attack. Options for prophylaxis include C1-INH concentrate and androgens.

Cinryze® (Shire, Lexington, MA) is a plasma derived C1 inhibitor used for prophylaxis in adults and adolescents. Clinical efficacy was reported in a randomized controlled crossover trial involving 22 patients with HAE [34]. Adverse reactions manifested as pruritis, rash, lightheadedness and fever. (34)

Danazol (an androgen) was first used for HAE in the 1970s and continues to be used today [35]. The exact mechanism is unknown but it is generally accepted that it increases C1-INH concentrations and enhances breakdown of bradykinin. In two RCTs, patients on danazol experienced significantly fewer acute attacks than those on placebo (p-values <0.001 for both studies) [36, 37]. It is generally well tolerated but can have serious side effects: hepatotoxicity, stroke, hypertension, lipid abnormalities, myopathies, abnormal menses, mood disturbances, and a masculinizing affect in females [35]. It is contraindicated in pregnant women and not recommended for use in children because it may result in premature epiphyseal closure.

CONCLUSION

Availability of acute and prophylactic treatments for HAE has expanded in the last 7 years. However there are no trials demonstrating superiority of one treatment over another. As such, it is advised that prescribers create an individualized treatment plan for patients with HAE [38]. Factors to consider while creating an individualized plan include age, gender, frequency and severity of attacks, and preference for home or facility administration. With the right drug and treatment plan, patients have the best opportunity to realize improvement in their quality of life and to avoid life-threatening complications.

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Disclosures

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