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Current and future therapies for the treatment of histamine-induced angioedema

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Abstract

Introduction—Angioedema, a sudden, self-limited swelling of localized areas of any part of the body that may or may not be associated with urticaria, is thought to be the result of a mast-cell mediated process versus a bradykinin etiology. Understanding the mechanism is key in determining the proper treatment.

Areas Covered—Clinical presentation of varying angioedema types may be similar; however, the appropriate treatment algorithm is dependent upon clinicians' knowledge of the underlying pathophysiology and classification of angioedema. Literature review of recent guidelines, available medications, and alternative therapies was completed to provide an overview of options.

Conclusion—There are no formal guidelines for treatment of acute or chronic histamine-mediated angioedema, and therefore, algorithms for the treatment of acute and chronic urticaria should be followed until such information becomes available. Differentiating histamine-mediated versus bradykinin mediated angioedema is essential, as treatments and treatment responses are quite different. Further research is needed to better understand idiopathic angioedema that is unresponsive to H1/H2 antagonists, LTMA, or medications designed to treat bradykinin-mediated angioedema.

Keywords

Angioedema; histamine-mediated; histamine; treatment; guidelines; pathophysiology; mechanism

1. Introduction

Angioedema (AE) is characterized as a sudden, self-limited swelling of localized areas of any part of the body involving the dermis, subcutaneous tissue, mucosa, and submucosa. It is often associated with urticaria in up to 50% of cases, and in these situations, the mechanism for these two processes are believed to be similar; however, isolated AE may also occur in

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Declaration of interest

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up to 10–20% of cases [1]. AE may be the result of histamine activation, bradykinin generation, or unknown pathophysiology. The clinical presentation of these types may be analogous in nature, but their treatment algorithms differ significantly. In this brief review, the definition, pathophysiology, and classification of histamine-induced AE and bradykinin-mediated AE will be summarized, with special attention given to evaluation, diagnosis, and management of the former condition.

2. Definition and epidemiology

AE is defined as a ‘transient, localized swelling of the dermis, subcutaneous tissue, mucosa, or submucosa’ that is present with urticaria in up to 50% of cases, though it may also occur in isolation in 10–20% of cases [1]. Urticaria involves the papillary dermis and mid-dermis of the skin, whereas AE affects the reticular dermis and subcutaneous or submucosal tissue [2]. Both conditions result in vascular leakage secondary to vasodilation and increased permeability. While patients with urticaria complain of intense pruritus, AE is often not pruritic and in some circumstances, is associated with pain and tenderness due to extreme distention of tissue and nerve fibers.

The prevalence of isolated AE is difficult to determine, as there is limited data available. Factors that thwart reliable epidemiological data pertaining to AE may include the reliance on ICD classification codes, which have unknown diagnostic sensitivity or specificity as the clinician’s diagnosis of AE, and designation of AE as a discrete condition or as part of a spectrum of allergic disorders, such as anaphylaxis and chronic urticaria is frequently very inconsistent [3]. Studies that have attempted to examine the epidemiology of AE have demonstrated, however, that it is not a rare disorder among emergency departments (ED) and hospitals. A retrospective review of all New York State hospitalizations from 1990 to 2003 revealed that AE was the most common non-asthmatic allergic disorder resulting in hospitalization [4]. Zilberberg et al. analyzed ED and hospitalization rates for AE in the USA in 2007 and found that there were at least 112,000 ED visits and 22,000 hospitalizations for AE in that year alone [5].

3. Pathophysiology

The mechanisms attributed to the development of AE include the following: mast cell or basophil activation, formation of bradykinin, or unknown etiology. The first two mechanisms are illustrated in Figure 1, and both of these may lead to the production of inflammatory mediators that disrupt vascular integrity. This disruption results in dilation and opening of cell-to-cell junctions of endothelial cells, which causes increased permeability of the venules and capillaries and resultant fluid extravasation. This fluid accumulates in the interstitial tissue spaces, presenting as non-pitting edema that most commonly affects the face, lips, tongue, throat, ears, hands and feet, and genitalia [6].

Figure 1(a) demonstrates the process in a type I IgE-mediated hypersensitivity reaction. Following allergen exposure (e.g. pollen, dustmite, cat), the allergen is first taken up by antigen presenting cells (APC) and then broken down into small peptides. These peptides are presented with major histocompatibility class 2 (MHC II) antigens on the cell surface, and

this MHC II-peptide complex is then recognized by T helper (Th) lymphocyte receptors. This interaction leads to T cell differentiation and activation of Th2 cells that release cytokines such as interleukin (IL)-4, IL-5, and IL-13. IL-4 is largely responsible for increased production of IgE and differentiation of B cells into plasma cells, which produce specific IgE antibodies capable of recognizing the original offending antigen. Other cytokines, such as IL-5, are important for promoting eosinophilic differentiation and migration leading to vascular inflammation. The specific IgE antibodies generated in response to an allergen bind to high-affinity IgE receptor FcεR1, and upon re-exposure to the specific peptide, cross-linking of specific IgE bound to the high-affinity IgE receptor FcεR1 causes mast cell or basophil activation and release of pre-formed and newly formed bioactive mediators. The most important pre-formed mediator is histamine, which binds to H1 and H2 receptors on blood vessels and leads to vasodilation and increased permeability [7].

Histamine-mediated AE may develop from an IgE-dependent reaction, direct activation of mast cells or basophils, interruption of arachidonic acid metabolism in mast cells, or augmentation of histamine release due to complement activation.

Nonspecific stimuli may also cause AE via direct activation of mast cells or basophils. Examples of these include opiates or radiocontrast agents. In the case of opiates, these medications bind directly to opioid receptors, which lead to release of mediators from mast cells or basophils. Radiocontrast media acts by altering the osmolality of the environment in which mast cells reside, and this change is also believed to cause histamine mediator release.

The third mechanism described for histamine-mediated AE can be explained by nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity reactions. NSAIDs inhibit cyclooxygenase (COX) 1 and 2 isoforms, which then blocks prostaglandin synthesis. This inhibitory response results in increased production of sulfidopeptide leukotrienes derived from the lipoxygenase pathway. The resultant imbalance between prostaglandins and leukotrienes enhances mast cell mediator release [8].

Finally, when one of the above mechanistic pathways is unable to explain the cause of AE, then it is referred to as idiopathic AE or AE of unknown cause. Complement activation is known to mediate mast cell or basophil histamine release through anaphylatoxin C5a in vasculitis/immune complex-associated urticaria [9]. A similar mechanistic process in the classical pathway of complement activation may also contribute to idiopathic histamine-mediated AE.

In bradykinin-mediated AE, the kallikrein–kinin cascade is activated when Factor XII (a.k.a. Hageman factor) binds to damaged tissue (Figure 1(b)). Factor XII is then converted to Factor XIIa, which then converts prekallikrein to plasma kallikrein. Bradykinin is produced when high-molecular-weight kininogen (HMWK) is cleaved by plasma kallikrein [2,3]. In binding to bradykinin 2 receptors, bradykinin causes vascular dilatation and increased permeability [10,11]. C1 esterase inhibitor (C1INH) serves as a regulatory enzyme for the contact system to prevent over production of bradykinin; however, when C1 esterase inhibitor (C1INH) is absent or decreased, dysregulation at multiple sites along the contact

pathway occurs, resulting in overproduction of bradykinin that manifests as AE [7]. Deficiency of C1INH may be due to a genetic mutation in the SERPING gene (hereditary AE), an autoantibody to C1INH, overconsumption of C1INH due to a lymphoproliferative disorder (acquired AE), or exogenous inhibition of C1INH (ACE inhibitor-induced AE).

For ACE inhibitor-induced AE, which occurs more frequently in African Americans in the USA, elevated levels of bradykinin are thought to be due to decreased catabolism of bradykinin as a result of a defect in kininase II, an enzyme which normally controls bradykinin levels [12]. In addition, aminopeptidase P (APP) degrades des-Arg9-BK, an active metabolite of bradykinin that binds to bradykinin1 receptors during inflammation, which may also result in increased bradykinin levels and lead to AE [13]. Finally, the neuropeptide substance P, released upon binding of bradykinin to bradykinin 2 receptors, can contribute to localized edema. Inhibition of angiotensin-converting-enzyme (ACE), as well as a defect in dipeptidyl-peptidase IV, prevents substance P degradation, leading to AE.

4. Classification

The pathogenesis of different AE conditions can often be determined by clinical presentation. As mentioned, the two general classes include bradykinin-mediated AE versus histamine-mediated AE. The bradykinin-mediated forms include hereditary AE (HAE), acquired AE, and ACE inhibitor-induced AE. Unlike HAE or acquired AE, in which C1INH plays a significant role, ACEI-induced AE is thought to be associated with defective degradation of vasoactive peptides such as bradykinin, des-Arg9-BK, and substance P, as described above [14].

In contrast, for histamine-mediated AE, a response may be generated in the setting of histamine release secondary to specific allergen exposure, direct mast cell or basophil activation by certain stimuli, mast cell mediator release due to prostaglandin and leukotriene imbalance, or possibly complement activation. Having a broad understanding of the classification and differential diagnosis of AE, is essential for ensuring that proper laboratory tests are ordered to confirm the diagnosis, as well as to avoid inappropriate, and often costly, therapies (see Figure 2 and 3).

5. Clinical presentation of histamine-mediated AE

While bradykinin-mediated subtypes of AE typically evolve over several hours, histamine-mediated AE tends to progress more rapidly and is associated with urticaria in up to 50% of cases [15]. Although this type of AE is more common in atopic individuals, it frequently manifests in the absence of atopy [2]. Swelling generally resolves within 24–48 h, but the characteristic wheal-and-flare eruptions of urticaria may be intermittent or persistent for weeks, months, or years without proper treatment interventions. Histamine-induced AE may be self-limited if the offending agent can be identified and avoided; however, most patients who experience recurrent episodes beyond six weeks are considered chronic, and determining an underlying cause in these individuals becomes even less likely. Table 1 provides a summary of the clinical features of different types of histamine-mediated angioedema.

6. Evaluation of histamine-mediated AE

Common causes of histamine-induced AE include foods, medications, stinging insect venoms, which includes fire ants, radiocontrast media, and NSAIDs. The most commonly implicated food allergens include milk, egg, shellfish, peanuts, and tree nuts; however, any food can potentially cause an AE episode. Despite this concern, routine food skin prick testing or specific IgE serologic testing to identify a latent food culprit is not recommended, unless the patient provides a history that is suggestive of a specific food being the causative etiology. Some patients may confuse true food allergy with mild mouth, tongue, or pharyngeal swelling, which is often experienced secondary to oral allergy syndrome. This syndrome is elicited by foods containing cross-reactive allergens in tree, grass, or ragweed pollen. For example, profilin in birch pollen cross-reacts with tree fruits like apple, and therefore, patients with birch tree pollen allergy may experience itching and swelling of the soft palate after eating raw apple that suggestive of an AE or soft tissue swelling sensation of the throat.ⁱⁱ [16]

Regarding medications, beta-lactam antibiotics are the most commonly identified agents in histamine-mediated AE, as they are extensively used in both the outpatient and inpatient settings. That being said, a spectrum of other therapies should be considered as an underlying causative agent when appropriate. The clinician has to have a basic understanding of which therapeutic agents are more likely to induce hives so as not to incorrectly advise patients to avoid important medications required to manage concomitant medical conditions, such as hypertension, hypercholesterolemia, diabetes mellitus, and osteoarthritis. For those patients who have had previous surgery or who are undergoing chemotherapy, perioperative anesthetic agents and chemotherapeutic agents (i.e. platins), respectively, should also be considered as causative agents when appropriate [17].

The initial assessment of histamine-induced AE should focus on the severity of symptoms. Vital signs should be monitored closely for circulatory collapse and/or respiratory distress. Oftentimes, this type of AE may present with other systemic symptoms, such as hives, difficulty swallowing, or shortness of breath. In the acute setting, it may be difficult to determine if AE is part of systemic anaphylaxis, and therefore, these patients should be evaluated and treated in an expeditious manner.

Once the patient has been stabilized, obtaining a thorough history is an essential part of the evaluation. Details regarding the physical signs and symptoms that occurred following exposure to the possible offending agent are helpful in elucidating whether or not a patient is experiencing histamine-mediated AE versus other forms of AE. Recognizing the time of onset to progression of symptoms may help to differentiate a histamine-associated process, which differs from a nonhistamine form of AE because the former evolves more quickly while the latter develops over several hours. It is also important to inquire about the presence of a family history of AE in order to exclude genetic forms of AE such as HAE. In addition to ruling out foods or medications, other conditions that should be excluded include thyroid disease, chronic infection, autoimmune disease, malignancy, and physical triggers (i.e. pressure, exercise, and vibration).

Laboratory evaluation assists in defining a histamine source versus other etiologies, especially when the history is unrevealing. It should include a focused, limited number of tests consisting of the following: complete blood count with differential, sedimentation rate, C-reactive protein, TSH, and complement 4 (C4) level. A serum tryptase level would only be useful during the first 4–6 h of an acute episode [18], unless there is suspicion that AE is a manifestation of systemic mastocytosis.

7. Management of histamine-mediated AE

The management of histamine-induced AE is dependent upon whether it is presenting acutely (<6 weeks) or chronically (>6 weeks).

7.1. Acute histamine-induced AE

The first step in treatment of acute histamine-mediated AE is removal of the offending agent. As previously stated, this type of AE may present in conjunction with anaphylaxis, and as such, priority should be given to airway management and prevention of circulatory collapse.

If systemic anaphylaxis is suspected, intramuscular (IM) epinephrine should immediately be administered. Epinephrine is a potent vasoconstrictor through alpha-adrenergic receptor and is capable of rapidly reversing peripheral vasodilation to lessen AE. Epinephrine also has beta-adrenergic effects that lead to bronchodilation and suppression of mast cells and basophils. The dose of IM epinephrine for adults ranges between 0.3 and 0.5 mg (1:1000 dilution or 1 mg/mL) administered in the thigh and for children, should be dosed at 0.01 mg/kg (up to 0.03 mg) [19]. A dose of epinephrine may be repeated every 20 min to once every 4 h as needed until control of symptoms has been achieved [20].

With respect to airway management, flexible laryngoscopy may be utilized to assess the extent of AE involving the airways [14] and the potential need for intubation; however, severe pharyngeal and laryngeal edema may make this procedure difficult [15,21]. Histamine-induced AE is less likely to result in the need for intubation, as it responds well to medications. This is in contrast to other nonhistamine-related forms of AE, such as HAE, acquired AE, and ACE inhibitor-induced AE, which are unresponsive to conventional medications and frequently require airway support if the AE involving the tongue and laryngopharynx is causing respiratory distress.

For acute histamine-mediated AE, oral, IM, or intravenous (IV) diphenhydramine has a rapid onset of action and assists in reducing swelling; however, it should be made clear that this medication should not be substituted for epinephrine if respiratory distress or anaphylaxis is the most significant concern. Another consideration may be the addition of H2 antagonists to H1 antagonists, as this combination may help prevent hypotension, urticaria, and pruritus. However, the scientific evidence supporting this latter intervention during an acute allergic emergency is not considered strong [22].

7.2. Chronic histamine-induced AE

Presently, there is limited evidence regarding the most effective management for chronic histamine-induced AE without urticaria. Treatment has largely followed guidelines established for the management of chronic urticaria, which often presents in conjunction with allergic AE. A stepwise treatment approach advocated for urticaria is summarized in Figure 4. There are some disagreements between the US and European treatment guideline steps and agents used for refractory cases of AE. For this manuscript, the discussion of treatment will focus on approaches advocated by the Joint Task Force Practice Parameter for treatment of acute and chronic urticaria with or without AE. The reader can refer to the reference by Fine et al. to gain a more in-depth understanding of treatment differences between US and European guidelines [23].

7.3. Histamine antagonists

Since histamine is considered the primary mediator causing histamine-induced AE, first-line therapy involves H1 antagonists. Second- or third-generation H1 antagonists are initially utilized because they are generally well tolerated with minimal side effects. Step 1 treatment recommends using one of these antihistamines (i.e. cetirizine, loratadine, fexofenadine, desloratadine, or levocetirizine) at standard FDA-approved doses [24,25]. Several randomized, controlled trials have demonstrated the effectiveness of these medications for treatment of urticaria with or without AE [26–33]; however, none of these medications have been investigated in controlled trials for the treatment of isolated histamine-mediated AE.

Few studies have compared the efficacy of various H1-antagonists in the treatment of urticaria, and none have examined their effect on management of isolated histamine-mediated AE. One randomized, double-blind study conducted by Handa et al. demonstrated that a higher percentage of patients experienced resolution of symptoms (52%) with cetirizine versus fexofenadine following one month of treatment [34]. Due to the paucity of head-on-head comparison studies between H1-antagonists, no specific recommendations regarding which second- or third-generation agent should be used as first-line treatment have been made for treatment of chronic urticaria or histamine-induced AE. Selection of these first-line agents are typically made based on side effects, cost, and patient preference.

For more severe cases of chronic urticaria and presumably histamine-associated AE, Step 2 therapy (Figure 4) recommends advancing H1-antagonist dosing up to 2–4 times the recommended FDA dose. Cetirizine has been shown to be of benefit at higher doses [35,36], but in one chronic urticaria study, increasing the dose threefold did not improve symptoms in more severe cases [37]. Staevska et al. found that a fourfold increase of levocetirizine and desloratidine were also effective in ameliorating chronic urticaria [38]. Of note, in this study, levocetirizine was found to be better at controlling hives that were not attenuated at comparable doses with desloratadine.

Although guidelines have recommended the addition of H2 antagonists if urticaria and/or AE is not controlled with H1 antagonists, high-quality randomized, controlled trials assessing this combination have not been completed. The mechanism behind the potential improvement in symptoms using H2 antagonists is thought to be secondary to a synergistic

effect with H1 antagonists, as studies have shown that circulating blood levels of the latter are increased in the presence of concomitant H2 antagonists [39]. It should be noted, however, that this effect was only seen with first-generation H1 antagonists, which utilize the hepatic microsomal system i.e. CYP2D6 or CYP2C9. Unlike that class, the second-generation antihistamines do not have a 'first pass' in the liver.

Use of first-generation antihistamines like diphenhydramine and hydroxyzine are also very effective for the treatment of chronic urticaria and histamine-mediated AE; nevertheless, caution should be exercised when using these agents, as they have significant anticholinergic effects and are able to cross the blood–brain barrier, causing impairment of cognitive behavior and motor coordination skills. If first-generation agents are used, they should initially be prescribed at low doses at bedtime. Use in older patients should be limited, as this population is more susceptible to the cognitive side effects of these agents. Titration of dosing should be based on treatment response and the patient's tolerance of unwanted side effects.

7.4. Leukotriene receptor antagonists

Leukotriene receptor antagonists (LTRA) are often added to H1-antihistamines when the latter are unable to adequately control symptoms. Studies regarding the efficacy of LTRAs in chronic urticaria have been relatively inconclusive, and these agents have not been evaluated in treatment of mast cell-induced AE. Montelukast and zafirlukast have been shown to be effective when compared to placebo in treatment of chronic urticaria in some studies [40,41]; however, other studies have not demonstrated a significant difference in utilization of these agents. For example, Nettis et al. demonstrated that the addition of montelukast to desloratadine contributed to a decrease in wheal number and pruritus, but the combination did not decrease the number of urticarial episodes [42]. Another study by Di Lorenzo et al. showed that the combination of the aforementioned medications did not offer any demonstrable improvement in urticaria [43]. It should be noted that in the latter study, patients who had positive autologous serum skin test (ASST) results, or who were aspirin intolerant, were excluded from the study. This may have biased their results, as previous studies found that LTRAs were more effectual for the treatment of chronic urticaria in patients with an ASST (suggestive of an FcER1 α subunit antibody) or who had a food additive or salicylate intolerance [44,45]. Finally, a study by Reimers et al. showed that zafirlukast did not offer any additional advantage over H1-antagonists [46]. Despite existing controversy regarding the performance of these medications in the treatment of chronic urticaria, clinical experience indicates that they can be useful in selected cases, and coupled with their excellent safety profile, have been recommended as Step 2 therapy. Again, it is important to emphasize that there are no clinical studies demonstrating the potency of LTRAs in the treatment of isolated histamine-induced AE.

7.5. Corticosteroids

There are currently no randomized controlled trials investigating the effectiveness of corticosteroids in the management of urticaria or histamine-mediated AE. Yet, systemic corticosteroids are often utilized to regulate severe exacerbations of chronic urticaria with or without AE, until combinations of less toxic maintenance medications can be found that

prevent recurrent exacerbations. Long-term use of oral corticosteroids is not recommended, but if required, they should be prescribed at the lowest possible dose. Caution using oral corticosteroids for extended periods of time should be exercised in patients with a previous history of intolerance of these agents, as well as in patients with diabetes, obesity, glaucoma, and osteoporosis.

7.6. Nonstandard therapies

The evidence for using alternative agents recommended as Step 4 therapy (Figure 4) for chronic urticaria with or without histamine-mediated AE, such as immunosuppressants, biologics, or anti-inflammatory medications, has been limited to case reports, case series, open-label studies, and in fewer circumstances, well-designed randomized, placebo-controlled trials with varying results. These interventions have more significant side effects, and their use should be determined on a case-by-case need, depending on the patient's underlying medical problems. For example, one would avoid cyclosporine in an individual with poorly controlled blood pressure, borderline kidney function, or hyperlipidemia, and hydroxychloroquine would not be an appropriate choice in a patient with preexisting retinopathy. Dapsone would not be utilized in a patient with glucose 6-phosphate deficiency.

Examples of some nonstandard oral medications that have been investigated in randomized, controlled trials include doxepin, ketotifen, and nifedipine. [47–49]. However, the size and results of these trials were highly variable, and patients frequently experienced side effects such as dry mouth, constipation, and lethargy.

There have been a number of studies examining the success of cyclosporine in the treatment of chronic idiopathic urticaria (CIU) unresponsive to H1-antagonists [50]. Cyclosporine acts by hindering cell-mediated immunity primarily through downregulation of T cell-dependent cytokine formation. Stellato et al. also showed that cyclosporine inhibits anti-IgE-induced histamine release from skin mast cells and human basophils *in vitro* [51]. Two randomized, placebo-controlled trials indicated that cyclosporine, in conjunction with H1-antagonists, was capable of treating CIU in patients with positive ASST results [52,53]. However, other studies found that the effectiveness of cyclosporine in CIU was not dependent on the presence or absence of an FcER1 α subunit antibody. Baskan et al. found that if cyclosporine did not achieve control of CIU after one month of treatment, continued use did not offer any increased advantage [54]. Use of cyclosporine requires regular monitoring of renal function, blood pressure, lipids, blood glucose, and signs of immune suppression manifesting as recurrent infections. Cyclosporine has not been investigated for the treatment of isolated histamine-induced AE, but it could be empirically tried if Step 1–3 therapies recommended by the urticaria guidelines are not effective in resolving the AE.

Although well-designed randomized, placebo-controlled clinical trials have not been completed to assess medications like dapsone, hydroxychloroquine, sulfasalazine, colchicine, tacrolimus, mycophenolate, or methotrexate, there are case reports, case series, and open-label trials that support the use of these drugs on an individual basis for treatment of chronic urticaria not responsive to Step 1–3 therapies. None of these agents have been investigated for histamine-mediated AE. The use of the aforementioned medications for the treatment of chronic urticaria is reviewed in detail elsewhere. Side effects related to some of

these drugs can be quite serious, and many require monitoring select blood tests regularly. For any medication, toxicity should be weighed against the potential benefits and patient preference.

Cases of chronic urticaria responding to therapies such as IV immunoglobulin (IVIG) and plasmapheresis have been reported, but the level of evidence supporting their use is low [55,56]. They are also generally intended to be transient interventions rather than chronic maintenance therapy. There is no evidence to support their use for AE.

Omalizumab (Xolair™) has been shown to be effective in severe, uncontrolled asthma in clinical trials [57,58], and is now approved for the treatment of CIU. Pivotal double-blind, placebo-controlled dose-ranging studies have found that omalizumab at 150 mg or 300 mg was sufficient in completely or partially controlling chronic urticaria unresponsive to H1 antagonists in over two-thirds of cases [59]. One recent randomized, controlled study in patients with CU and AE showed that 70% of patients in the omalizumab group experienced resolution of urticaria and 77.8% of patients experienced complete resolution of AE with 24 weeks of therapy [60]. Therefore, omalizumab may have a role in histamine-induced AE associated with chronic urticaria, but further examination is required to determine if it could also be an effective intervention for isolated histamine-induced AE not responsive to H1-antagonists.

Recently, a systematic literature review was conducted by van del Elzen et al. in order to explore management options for non-hereditary AE cases, including ACE inhibitor-induced AE, AE with wheals (chronic spontaneous urticarial), and idiopathic AE [61]. For the second type, omalizumab was noted to be the most effective for refractory cases. In the case of idiopathic AE unresponsive to high-dose H1-antihistamines and oral corticosteroids, licensed HAE drugs such as icatibant or ecallantide were shown to be beneficial forms of treatment, however, it was acknowledged that the utilization of these drugs was off label, and the beneficial effects were mainly seen in patients refractory to multiple treatment options recommended to histamine-mediated AE. The uncertainty of whether to continue using alternative treatments directed toward histamine-induced AE or shift to therapies targeted for bradykinin-mediated AE emphasizes the need for diagnostic biomarkers that can differentiate between the pathomechanisms of these two conditions.

8. Conclusion

Histamine-induced AE, which may occur through multiple mechanisms, is important to differentiate from other forms of AE, as the treatment approach and prognosis for this condition is quite different. The current management strongly relies on guidelines developed for chronic urticaria, as there is a paucity of literature investigating allergic AE as a distinct clinical entity. In the acute setting, regardless of whether the patient presents with isolated AE involving the upper airway, or in conjunction with multiple organ system involvement suggestive of systemic anaphylaxis, IM epinephrine should be administered as first-line treatment. Another important factor is avoidance of identifiable offending triggers. If these triggers are unable to be established, H1/H2-antihistamines and leukotrienes should be prescribed.

For recurrent episodes of isolated histamine-induced AE, clinicians should follow the current step-care treatment algorithm advocated by recent evidence-based chronic urticaria guidelines. Most of these treatment recommendations for chronic urticaria have not been studied for histamine-mediated AE. Nonetheless, since AE is associated with chronic urticaria in 40% of cases and most likely has a similar mechanism of action, this approach seems reasonable.

In cases of histamine-induced AE resistant to Step 2 therapy, it is important to exclude any causes of bradykinin-mediated AE. Once excluded, although it may still not be clear whether to follow the CU or non-histamine-mediated AE treatment algorithm, it is recommended to first follow Step 4 therapy by adding cyclosporine, omalizumab, or one of the other anti-inflammatory agents, depending on the case profile and patient preference (Figure 4). For any treatment recommendation, the risk of toxicity versus clinical benefit of using immunosuppressant agents, anti-inflammatory agents, or biologics should carefully be discussed with the patient. Immediate divergence to therapies approved for bradykinin-mediated AE in patients with AE unresponsive to H1/H2 antihistamines and LTMA is associated with significant cost. Given the lack of mechanistic evidence supporting the use of approved HAE treatments for refractory idiopathic AE, their use needs to be carefully considered before prescribing them. An exception would be whether the patient met the current diagnostic criteria for HAE with normal complement with or without a Factor XII mutation [62].

Regardless, it is clear that there is a strong underlying need for further research analyzing the mechanistic pathways of idiopathic AE uncontrolled by conventional regimens in order to identify diagnostic biomarkers and targeted therapies that would improve the management of this condition.

9. Expert opinion

Acute AE can be difficult to differentiate from acute anaphylaxis in many patients, and therefore, management relies on securing an airway and treatment with medications used for AE associated with urticaria, or anaphylaxis, in order to stabilize the patient. These therapies include H1 antagonists and if indicated, epinephrine. Referral to an allergy specialist is appropriate for further workup. When episodes are recurrent over a period of more than 6 weeks, AE is then referred to as chronic. Attempts to rule out underlying causes for both acute and chronic urticaria, such as medications, foods, or underlying clinical disorders, should be attempted. However, similar to acute and chronic urticaria, unless there is a clear or potential cause identified through the history, an extension workup is not recommended. Limited blood testing may include a CBC with differential, sedimentation rate, thyroid-stimulating hormone and a complement 4 level. Treatment should follow the same algorithm recommended for chronic urticaria with or without AE, and if necessary, second- or third-generation H1 antagonists may be increased up to four times the recommended dose. Additional therapies such as H2 antagonists and leukotriene-modifying agents, both of which are safe, may further help to prevent recurrent swelling episodes. Skin or serologic testing to aeroallergens is not recommended unless the patient complains of concomitant rhinitis symptoms, thus requiring a separate workup unrelated to AE. Skin or serologic

testing to foods is also not recommended unless the patient relates the onset or recurrence of the swelling to particular foods. Patients unresponsive to these therapies should be excluded for bradykinin-mediated forms of AE. There is little evidence in the literature that provides guidance on how to treat AE unresponsive to first-line therapies. It is recommended that the US or European guidelines for chronic urticaria treatment be followed in refractory AE cases. There is no evidence to support use of hereditary AE (HAE)-type medications for these idiopathic AE patients. Further research is required to better understand the pathomechanisms and to develop biomarkers for non-HAE cases unresponsive to H1 antagonists and other therapies recommended for histamine-mediated AE.

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Article highlights

- Angioedema presents as a sudden onset of localized swelling
- Angioedema can be histamine mediated or bradykinin mediated; treatments and treatment responses differ between these two groups
- Angioedema in the acute setting can be difficult to differentiate from anaphylaxis and therefore should be treated accordingly until proven otherwise
- The history is the best resource for identifying an underlying cause
- If angioedema episodes persist greater than 6 weeks then they are chronic
- Treatment chronic histamine mediated idiopathic angioedema should follow the current US or European guidelines for treatment of chronic urticaria as no guideline are available for isolated non-HAE angioedema
- All patients presenting with isolated angioedema should have a C4 level to exclude bradykinin mediated angioedema
- More research is required to better understanding idiopathic non-HAE angioedema unresponsive to first line agents like H1- and H2-antagonists and leukotriene modifying agents.

This box summarizes key points contained in the article.

(a) Mast cell Activation (b) Contact Pathway Activation

Figure 1.
Pathogenesis of Mast Cell.

Figure 2.
Classification of Angioedema.

Figure 3.
Treatment Algorithm For Chronic Urticaria Proposed For Allergic Angioedema.

Figure 4.
Algorithm to assess urticaria and/or angioedema.

Table 1

Clinical and diagnostic features of different types of mast cell-induced angioedema.

Angioedema type/mechanism	Clinical and diagnostic features
Angioedema due to IgE-dependent reaction	Angioedema often accompanied by urticaria and pruritus; Occurs upon exposure to specific allergens (e.g. environmental allergens, foods, medications; Lasts for 24–48 h; Responsive to antihistamines and corticosteroids.
Angioedema from direct activation of mast cell	Angioedema associated with stimuli such as opiates or radiocontrast agents
Angioedema with urticarial vasculitis	Angioedema accompanied by urticaria; May have petechiae or purpura after swelling resolves; Symptoms of underlying vasculitis
Angioedema due to leukotriene and prostaglandin imbalance	Typically present with urticaria; Most common example is NSAID hypersensitivity
Idiopathic histaminergic angioedema	Angioedema sometimes accompanied by urticaria; swelling may persist for up to 48 h; responsive to antihistamines and corticosteroids

Adapted from Bernstein JA and Moellman JJ. Emerging concepts in the diagnosis and treatment of patients with undifferentiated angioedema. *International Journal of Emergency Medicine* 2012; 5:39.