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Angioedema-Diagnosis & Management

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Abstract

Angioedema (AE) encompasses a diverse range of conditions categorized into three main groups: (1) angioedema mediated by histamine (AE-H); (2) angioedema mediated by bradykinin (AE-BK); and (3) angioedema with an unknown mechanism (AE-UNK). It can manifest on any part of the body, though commonly affected areas include the face, lips, mouth, throat, larynx, extremities, genital regions, and gastrointestinal tract. AE-H can occur by itself or in conjunction with chronic urticaria, the acute form can be allergic due to food, drug, or insect bite related and patients often respond with antihistamines. Drug used angioedema is caused by increased production or decrease breakdown of vasoactive peptides, mainly bradykinin. Angiotensin converting enzyme inhibitor (ACE-I), Dipeptidase-IV (DPP-IV) inhibitor reduce the breakdown of bradykinin and substance P (SP). Hereditary angioedema (HAE) is defined by reduced functionality of the C1-inhibitor (C1-INH) protein, attributed to either its deficiency (Type I) or dysfunction (Type II). Additionally, there exist alternative types of HAE where C1-INH activity remains normal, yet the condition is linked to genetic mutations in different genes, such as factor XII. Acquired angioedema (AAE) can be distinguished from other types of angioedema; common in old age, a low functional & quantitative C1-INH level, Low C1q, presence of C1-esterase inhibitor antibodies and underlying lymphoproliferative diseases or both. There is a need for improved diagnostic methods for patients with idiopathic histaminergic acquired angioedema (IH-AAE), Idiopathic non-histaminergic acquired angioedema (InH-AAE), as well as angioedema induced by ACE inhibitors, and hereditary angioedema (HAE) with normal C1-INH levels. This review will discuss the classification, pathophysiology, and management of angioedema.

Keywords: Angioedema (AE), angioedema mediated by histamine (AE-H), angioedema mediated by bradykinin (AE-BK), Histaminergic angioedema, bradykininergic angioedema, Hereditary angioedema (HAE), Acquired angioedema (AAE), unknown mechanism angioedema (AE-UNK), Idiopathic angioedema, C1-inhibitor, C1-INH, Icatibant, Ecallantide, tranexamic acid

INTRODUCTION

Hippocrates initially referred to organ swelling as oedema, but it wasn't until the 1800s when Quincke formally recognized it as a medical condition through a published series of cases. Subsequent clinical observations and scientific progress revealed that angioedema can mechanistically involve pathways mediated by either bradykinin or histamine and leukotrienes. Angioedema (AE) is an acute asymmetrical, non-pitting localized swelling of mucosa, submucosa, or sub-cutaneous tissue of skin due to increase in vascular permeability of blood vessels [1].

Angioedema affects areas characterized by loose connective tissue, including the face, lips, oral cavity, throat, voice box, uvula, limbs, genitals, and digestive tract. Swelling commonly occurs around the lips and eyes (peri-orbital). Swelling in the upper airway, particularly laryngeal edema, poses a potential life-threatening risk, while severe swelling

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in the pharynx and tongue can also have devastating consequences. Angioedema is principally categorized into angioedema mediated by histamine (AE-H) and angioedema mediated by bradykinin (AE-BK). 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 the cases, CSU with AE in 40% of the cases, and isolated AE in up to 20% of cases. [2,3] Acute episode of angioedema without urticaria characterized by AE-BK, may be hereditary, acquired, drug-induced or may be due to infections such as Herpes Simplex Virus, Coxsackie A&B virus, Hepatitis B Virus, Ebstein Barr Virus etc. [4].

NSAID, ACE-I, beta-lactam antibiotics, and neprilysin-inhibitors impair bradykinin metabolism. DPP-4 inhibitors and Substance P (SP) reduce breakdown of bradykinin. Hereditary angioedema (HAE) is an uncommon genetic condition, occurring globally at an estimated frequency of 1 in 40,000 to 1 in 50,000 individuals. AE-BK does not respond to drugs that AE-H does, like antihistamines (AH), oral corticosteroids (OCS), or injection adrenaline. In sever and life-threatening cases of BK-mediated AE, C1-INH concentrate, Bradykinin Type 2 receptor (B2R) antagonist (Icatibant), Tranexamic acid have proven to be effective therapy [5-7].

Classification of Angioedema

The classification of angioedema primarily relies on clinical characteristics, genetic analysis, and treatment response. It is determined by the endotype (arising from an excess of bradykinin, activation of mast cells/basophils, or of uncertain origin), or by the phenotype and genotype (either acquired or inherited, with or without a deficiency of C1 inhibitor [C1-INH]). These classifications establish three main categories: (1) angioedema mediated by histamine and/or other mast cell- and basophil-related factors (AE-H); (2) angioedema mediated by bradykinin (AE-BK); and (3) angioedema with an unknown underlying mechanism (AE-UNK). (Figure 1) [8,9].

In AE-H, the occurrence of itching serves as a significant distinguishing characteristic from AE-BK. The itching sensation arises from the activation of specific histamine-sensitive unmyelinated c-fibers by histamine.

Common triggers for angioedema include allergens such as certain foods like shellfish or nuts, medications, and insect stings. Symptoms typically develop rapidly, usually within minutes to an hour after exposure to allergens. The duration of symptoms is usually brief, and swelling commonly affects the skin and mucous membranes, including areas like the face, lips, eyes, and hands.

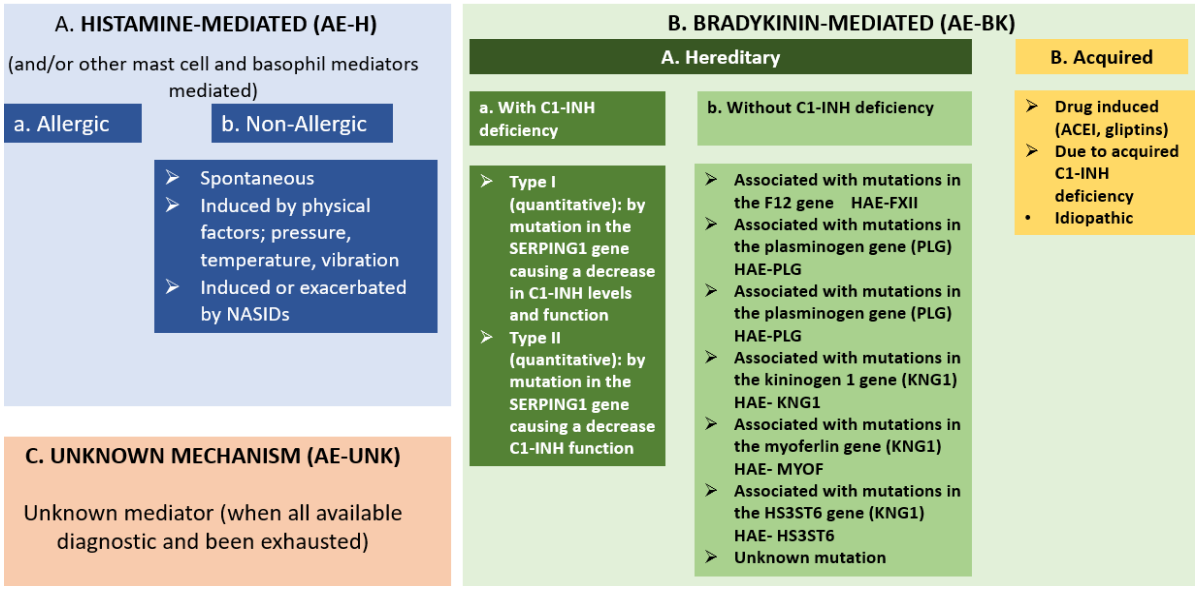

Figure 1. Classification of angioedema.

Table 1. Clinical differences between Histamine mediated angioedema (AE-H) and Bradykinin mediated angioedema a(AE-BK).

Clinical features	Histamine mediated	Bradykinin mediated
Possible agents (Foods, drugs, insects, animal, dander, aeroallergens, and others)	May be present	ACEI, DPP-IV inhibitors, NEP inhibitors, estrogens for HAE
Age of onset	Any age	3-20 years for HAE
Family history	Rare	Present in 75% for HAE Non for HAE
Swelling	Quick onset (minutes), recovers faster (12-24 hours)	Develops slowly (hours) recovers slowly (48-72 hours or more)
Severity	Less severe	More severe
Urticaria	Often	Absent
Risk of recurrent laryngeal edema	Low	Significant
Recurrent abdominal attacks	Rare	Frequent
Prodromal symptoms	None	May precede (Frequent in HAE)
Response to anti-histamines, corticosteroids, and adrenaline	Excellent	Poor

ACEI=Angiotensin converting enzyme inhibitor, NEP= Neutral endopeptidase, HAE=hereditary angioedema

The patients usually respond to treatment by antihistamines (AH), oral corticosteroids (OCS), or injection epinephrine. AE-BK generally shows no symptoms (non-itchy) until puberty, but it can manifest with gastrointestinal symptoms like vomiting and diarrhea. Factors that can trigger angioedema include intense physical activity, drinking alcohol, emotional stress, and physical injury. The primary areas affected on the skin are the face, hands, arms, legs, genital area, and buttocks. Involvement of mucous membranes typically occurs in the tongue, throat, or larynx. There are considerable group of patients where differentiation between AE-H and AE-BK is challenging because of pathophysiological overlap which is determined by the bi-directional connection between the mast cells/ basophils, and the kallikrein-kinin system (Table 1).

PATHOPHYSIOLOGY OF ANGIOEDEMA

Histamine-Mediated Angioedema (AE-H)

The primary mechanism behind histamine-mediated angioedema (AE-H) is a type I immunological response. In the sensitization phase of this reaction, exposure to allergens like food allergens (e.g., milk or nuts) prompts an increase in the production of allergen-specific immunoglobulin E (IgE) by plasma cells due to activation of B lymphocytes. During sensitization, IgE molecules attach to high-affinity FcϵRI receptors, which are consistently present on effector cells (mast cells and basophils). Upon re-exposure to the same allergen, IgEs cross-link with the allergen, prompting the degranulation of effector cells and initiating the "early phase" of the immunological reaction.

This degranulation releases inflammatory mediators such as histamine and serine proteases (e.g., tryptase and chymase), which disrupt vascular integrity. This disruption leads to vasodilation and increased capillary permeability, resulting in fluid accumulation in interstitial tissue spaces, causing non-pitting edema, notably in areas like the face, ears, throat, tongue, lips, hands, feet, and genitalia [10-12].

In contrast to early-phase reactions, the cutaneous manifestations of a late-phase reaction involve the accumulation and infiltration of eosinophils, neutrophils, CD4+ T cells, and basophils. Late-phase reactions occur more slowly, typically manifesting after 1-6 hours. Apart from type I immunological reactions, histamine-mediated angioedema can also occur due to direct mast cell or basophil activation, leading to the release of inflammatory mediators. This direct activation can arise from internal or external factors such as anaphylatoxins (e.g., complement fragments C3a, C4a, and C5a) or MRGPRX2,

which cause direct mast cell activation and degranulation by binding to non-FcεRI receptors on mast cell membranes. Iodine- and gadolinium-based contrast agents are examples of external factors that act directly on mast cell and basophil membranes to induce degranulation [13-15].

Furthermore, disruption of the arachidonic acid pathway may contribute to histamine-mediated angioedema. A notable example is NSAIDs-induced urticaria/angioedema (NIUA). Nonsteroidal anti-inflammatory drugs (NSAIDs) strongly inhibit cyclooxygenase-1 enzymes (COX-1), disrupting the arachidonic acid pathway, leading to increased production of eosinophils, mast cells, and proinflammatory mediators. This, in turn, results in increased production of cysteinyl leukotrienes, a family of inflammatory lipid mediators, leading to increased vascular permeability and subsequent angioedema [16-19].

Bradykinin-Mediated Angioedema (AE-BK)

The primary enzymes responsible for the production of bradykinin are activated factor XII and plasma kallikrein, both of which are regulated by C1-INH. Elevated levels of bradykinin have been detected in patients with hereditary angioedema (HAE) during episodes of swelling, affirming its role as the cause of the swelling. Bradykinin was identified as the sole vasoactive peptide present in the plasma of individuals with HAE [20-24]. C1-INH serves various roles pertinent to bradykinin production, such as inhibiting factor XIIa, plasma kallikrein, and coagulation factor XIa. Additionally, it contributes to regulating complement activation.[25].

There is excessive bradykinin production because of deficiency of C1-INH enzyme. [21,26] Factor XII possesses a limited enzymatic capability, but it's adequate to kickstart the bradykinin-forming process upon interaction with negatively charged large molecules [27]. Once activated, factor XIIa can trigger factor XI activation, perpetuating the intrinsic coagulation pathway, and can also transform plasma prekallikrein into kallikrein. Subsequently, kallikrein breaks down high molecular weight kininogen (HMWK) to release bradykinin. [21,27] Plasma kallikrein swiftly converts factor XII into factor XIIa, creating a positive feedback loop that enhances cascade activation. (Figure 2). [28] Furthermore, there exists a fibrinolytic pathway where kallikrein, factor XIa, and factor XIIa convert plasminogen into plasmin. This pathway holds significance in the context of bradykinin-mediated angioedema, particularly in hereditary angioedema with normal C1-INH activity, as plasmin has the ability to cleave and activate factor XII, thus contributing to the bradykinin-forming cascade.[29] The diagnostic procedure for HAE (Type I and Type II) needs measurement of both C1-INH inhibitor serum concentration and function, while for HAE Type III is diagnosed by factor XII mutation (Figure 3).

DIAGNOSIS OF ANGIOEDEMA

(Figure 4 and 5) One of the most important to diagnose angioedema is to separate AE-H from AE-BK and to exclude other pathologies such as infection, tumors, and diseases of large salivary glands. The healthcare provider needs to determine whether the patient presents with symptoms like hives, a rash, itching, bronchospasm, or low blood pressure, as these indicators help to narrow down the assessment for histamine-mediated angioedema (AE-H). Common triggers for AE-H include allergic reactions to food, medications, physical contact, or insect bites, which may lead to anaphylaxis. While a high level of serum tryptase can support the diagnosis of anaphylaxis, normal levels are not sufficient to rule it out. Ocular swelling accompanying symptoms like rhinitis and conjunctivitis is often due to airborne allergens. In patients with recurrent angioedema without urticaria or pruritus; one should specifically suspect AE-BK and encompass ACE inhibitors.[30] C1-INH Hereditary angioedema (HAE) or C1-INH acquired angioedema (AAE). A first suspicion of C1-INH HAE is given by mucosal swelling and / or unclear abdominal pain in patients at a young age and those with a family history, a lack of concomitant drug therapy and the absence of urticaria as well. Diagnosing hereditary angioedema (HAE) can be particularly challenging, as a significant portion of patients (6-25%) with C1-INH HAE may not exhibit symptoms in their family members. Additionally, it's notable that 5-10% of individuals with C1-INH HAE lack mutations in the SERPING1 gene, while 5% of those with mutations may not display symptoms. Initial testing for suspected C1-INH HAE or acquired

angioedema (AAE) typically involves measuring the concentration and function of complement components C4 and C1-INH. In cases where patients are middle-aged at symptom onset or lack a family history, evaluating C1q concentration is advised to identify C1-INH AAE. However, diagnosing idiopathic histaminergic acquired angioedema (IH-AAE), idiopathic non-histaminergic acquired angioedema (InH-AAE), ACE inhibitor-induced angioedema (ACEi-AE), and non-C1-INH HAE can be even more challenging due to the absence of standard biochemical laboratory tests. InH-AEE and AE-UNK both are idiopathic disorders, and their mechanisms are incompletely clarified.[31] In C1-INH HAE, symptoms occur earlier in patients while in AE-UNK, symptoms start during young adulthood and in InH-AAE, symptoms appear in late adulthood. Face and tongue are most commonly involved in idiopathic disorders. Additionally, it's important to rule out other uncommon conditions such as Crohn's disease affecting the mouth and lips, facial cellulitis, and superior vena cava syndrome.

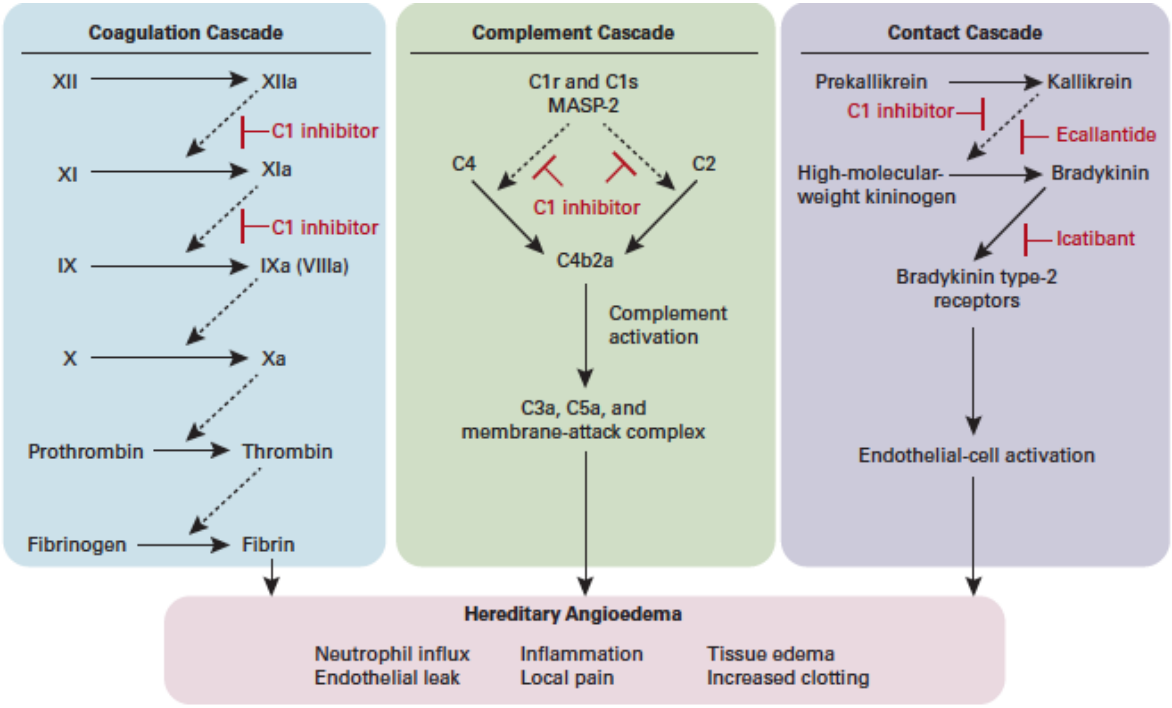

Figure 2. Coagulation cascade.

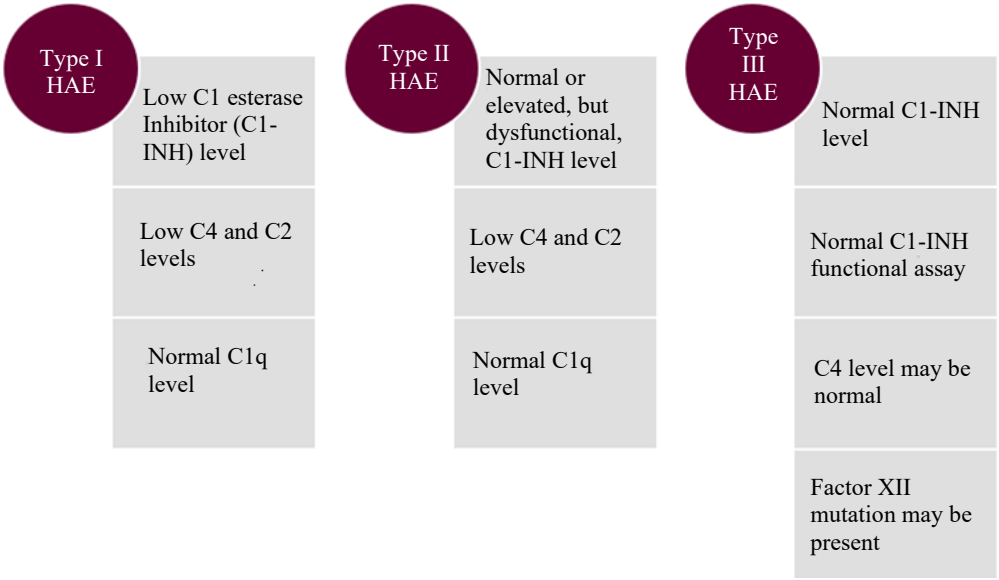

Figure 3. Classification of hereditary angioedema (HAE).

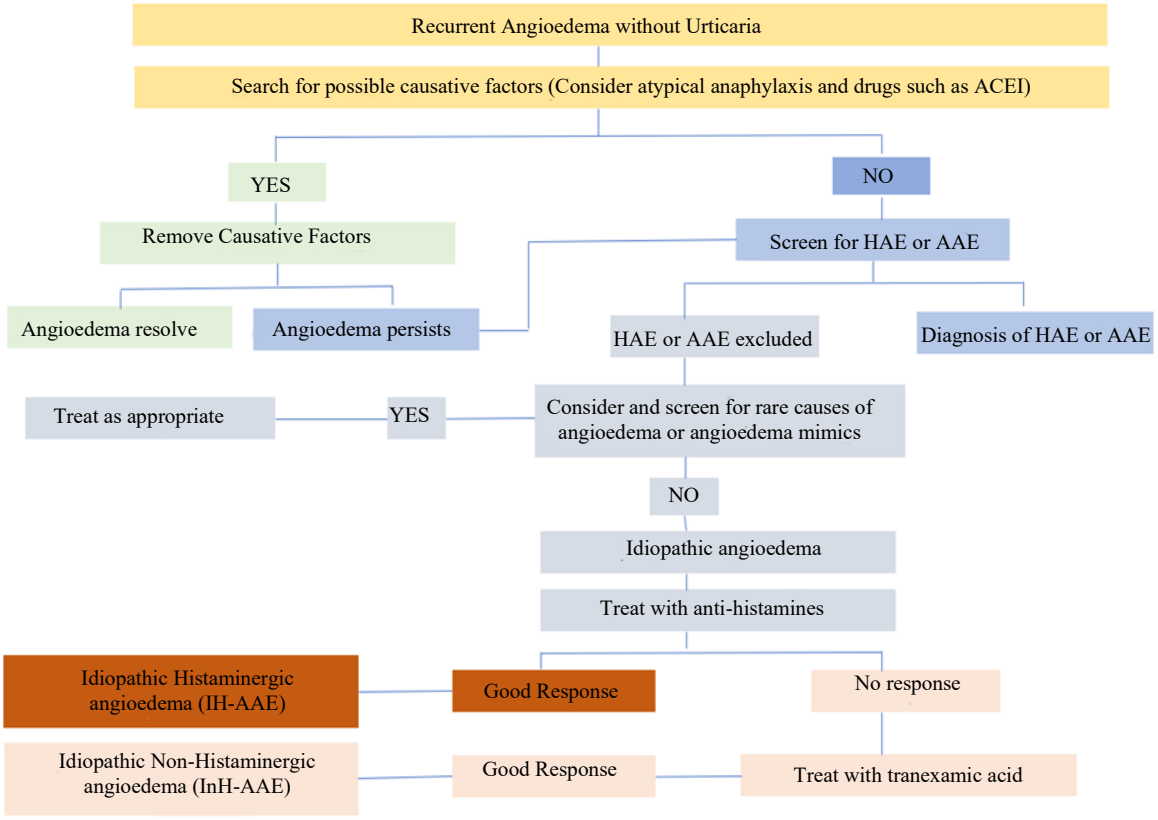

Figure 4. Diagnostic algorithm of recurrent angioedema.

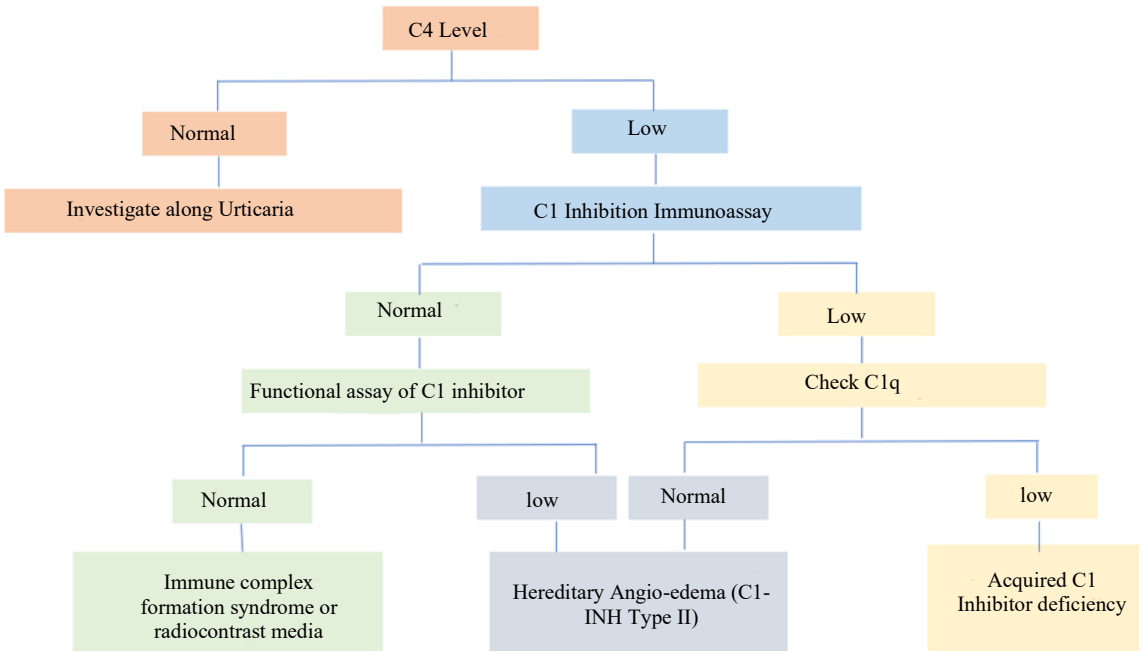

Figure 5. Diagnostic algorithm of HAE.

MANAGEMENT OF ANGIOEDEMA

Management of Histamine-Mediated Angioedema (AE-H) without Airway Compromise

Severe angioedema can often be prevented by avoidance e.g., patients with cold urticaria should not swim in cold water. Tolerance treatment has been reported to be successful [30]. This treatment involves repeated exposure of skin to the specific provoking factor until a state of tolerance has developed. The

frequency of exposure is then gradually reduced to the point at which reactivity to the physical stimulus begins to occur. Systemic antihistamine may be effective in reducing the itching associated with angioedema caused by physical stimuli. 1st generation antihistamines for acute AE (cause drowsiness): oral doxepin may be effective for AE (10-25 mg at bedtime), older children and adults: hydroxyzine (5mg/mL)10 -25 mg thrice a day, or diphenhydramine 25-50 mg q6h, and 2nd generation H1 blockers: fexofenadine 180 mg/d b.i.d., loratadine10 mg/d, cetirizine 10 mg/d, desloratadine 5mg/d; use with caution in pregnancy and in the elderly.

Management of Histamine-Mediated Angioedema (AE-H) with Airway Compromise

It is important to ensure a patent airway first. Adrenaline should be administered; it may be given as self-injection by the patient. Adrenaline may abort the acute attack. If adrenaline does not work intravenous antihistamines and hydrocortisone should be given under close observation in intensive care unit [32]**.**

Onset of Reaction

- Injection epinephrine 0.5 mg intramuscular (IM) stat
- Injection clementine 2 mg IV stat or oral bilastine 20-40 mg stat
- Injection hydrocortisone 200 mg IV stat or solumedrol 40 mg IV stat or oral methylprednisolone 16 mg stat

Impending Respiratory Failure

- Epinephrine 1:1,000, 0.3 ml IV
- Sedation (Injection dexmedetomidine / Injection ketamine
- Nasal intubation with Bronchoscope or Front of neck -airway access by Frova stylet & endotracheal tube (6mm) or surgical tracheostomy / mechanical ventilation

Management of Drug-Induced Angioedema

Angiotensin Converting Enzyme Inhibitor-Induced Angioedema

Discontinuation of angiotensin-converting enzyme inhibitor (ACEi) is recommended for any patient with prolonged use experiencing even mild angioedema. While in mild cases, discontinuing ACEi may suffice to manage the issue, intravenous administration of antihistamines and steroids is frequently necessary, sometimes requiring repeated doses. When laryngeal edema occurs, inhaled, subcutaneous or intravenous adrenaline should be given. The dose of subcutaneous adrenaline is 0.01 ml per kg body weight of 1:1000 aqueous adrenaline and it may be repeated every 15 to 20 minutes as needed oral or nasal intubation tracheotomy or retrograde intubation over a guide wire through the cricothyroid membrane may be needed under close observation [**33**]. Intravenous saline infusion should be started if hypotension is present. The progression of the condition can be uncertain, with angioedema potentially worsening swiftly. Initial treatment may yield inadequate results, particularly if the angioedema is already firmly established. In general, the angioedema resolves after one to two days and does not recur if the angiotensin converting enzyme inhibitor is withdrawn. A medic alert bracelet is useful and clear instruction about the avoidance of angiotensin converting enzyme inhibitors should be given to the patient and other doctors involved in the care of the patient. Once the condition stabilizes, the patient can be released from the hospital with a brief prescription of oral antihistamines and a gradual reduction of oral corticosteroids.

Non-Steroidal Anti- Inflammatory Drug-Induced Angioedema

The suggested mechanisms involve inhibiting cyclo-oxygenase, which results in increased mast cell degranulation and heightened production of lipoxygenase products. It is essential for the patient to avoid the offending drug and the whole group of nonsteroidal anti-inflammatory drugs in the future.

Management of Hereditary Angioedema (C1-INH HAE)

For mild to moderate episodes, only symptomatic treatment is recommended. However, if the attack is severe or life-threatening, long-term preventive measures are necessary. With the advent of

serological testing and modern drugs, provided an early diagnosis and treatment is initiated, the duration of attack can be reduced to 1-3 hours from 3-5 days and can improve the quality of life [**34].**

On-Demand Treatment of Acute Attack of HAE (Figure 6)

The on-demand treatment of HAE attack is recommended to perform using any of the following agents [35-38]:

1. C1-INH concentrate
2. Icatibant, a synthetic bradykinin beta2 receptor antagonist
3. Ecallantide, a recombinant plasma kallikrein inhibitor
4. Fresh frozen plasma (FFP), if '1-3' not available

Acute HAE Treatment

- **C1 INH concentrate IV**, dosed at 1,000 units if <50 kg; 1,500 units if 50- 100kg; 2,000(units if >100 kg [a pasteurized human pd C1 INH (berinert), dosed at 20 units/kg (available in 500 units/10 ml, max infusion rate of 4 ml/min IV via peripheral vein. DO NOT SHAKE (will denature the protein)].
- **Kalbitor (Ecallantide)**, a kallikrein inhibitor, is dosed in patients more than 16 years old at 30 mg SC with 3 separate 10 mg/ml injections in the abdomen, thigh, or upper arm and the second 30-mg dose may be repeated within 24 hours if needed.
- **A bradykinin receptor-2 antagonist (Icatibant)**, dosed SC and supplied in a prefilled 3-ml syringe for home administration approved by food and drug administration (FDA) advisory [35-38].

Short-term prophylaxis (STP) (Figure 7)

The preferred option for short-term prophylaxis is either plasma-derived C1-inhibitor (pd-C1-INH) or recombinant C1-inhibitor. This should be considered for patients undergoing medical procedures, surgery, or situations that heighten the risk of an angioedema attack, especially when manipulation of the upper airway is involved. [35-38]

- For any surgical procedure, whether elective or emergency (such as gall bladder or head & neck surgery), the preferred medication is pd C1 inhibitor concentrate. Alternatively, Solvent Detergent Reacted plasma (SDP) or Fresh Frozen Plasma (FFP) should be administered 1-6 hours prior to the procedure at a dosage of 10ml/kg (400 – 800ml in adults).
- *Minor procedures (dental work):* if C1 INH is available, no prophylaxis; otherwise: danazol 2.5 -10 mg/kg/d (maximum 600 mg/d), stanozolol 4-6 mg/d, for 5 days prior to and 2-5 days after surgical intervention.
- *Major procedures (including intubation):* C1 INH1 concentrate given 6 hours prior with additional dose during procedure. If unavailable, danazol 2.5 -10 mg/kg/d (max 600mg/d). In situations where solvent/detergent treated plasma (SDP) is not accessible, fresh-frozen plasma (FFP) can be administered at a dosage of 10mL/kg or 2-4 units (400-800 ml) 1-6 hours prior to the procedure in adults.

Long Term Prophylaxis (LTP) (Figure 8)

For long-term prophylaxis (LTP) of hereditary angioedema, treatment options include lanadelumab (a monoclonal antibody targeting plasma kallikrein), plasma-derived C1 inhibitor (pd-C1-INH) administered intravenously (IV) or subcutaneously (SC), or berotralstat (an oral, synthetic, small-molecule plasma kallikrein inhibitor). If these options are not available, attenuated androgens can be considered, with tranexamic acid being a last-resort treatment. Despite being on LTP, patients may still experience acute attacks, so they are advised to keep two doses of on-demand treatment available. On-demand therapy typically involves administering nano-filtered plasma-derived C1 inhibitor concentrate (pd-C1-INH) or anti-kallikrein inhibitors such as ecallantide, as well as a bradykinin beta 2 receptor antagonist as icatibant.

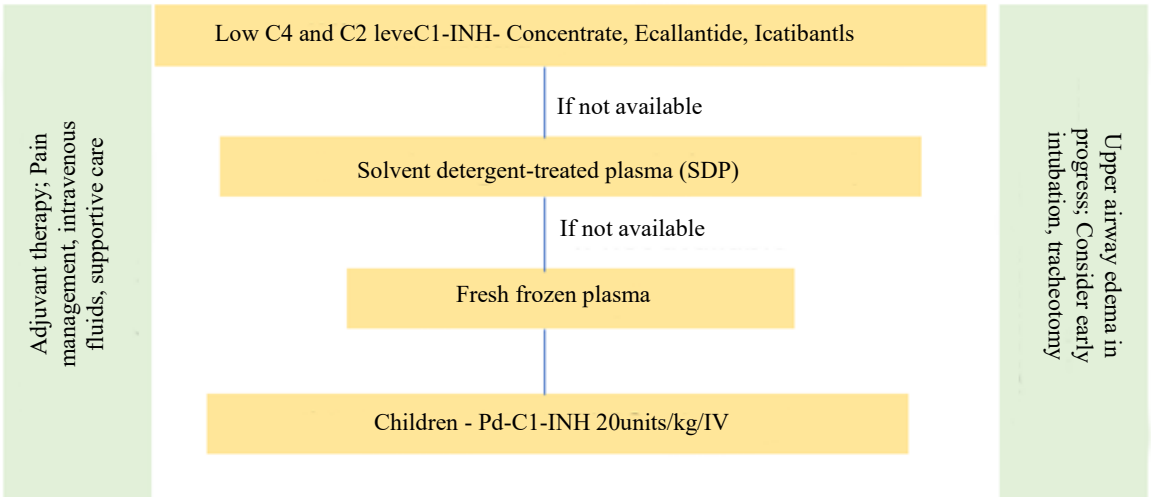

Figure 6. Treatment of Acute Attack of HAE.

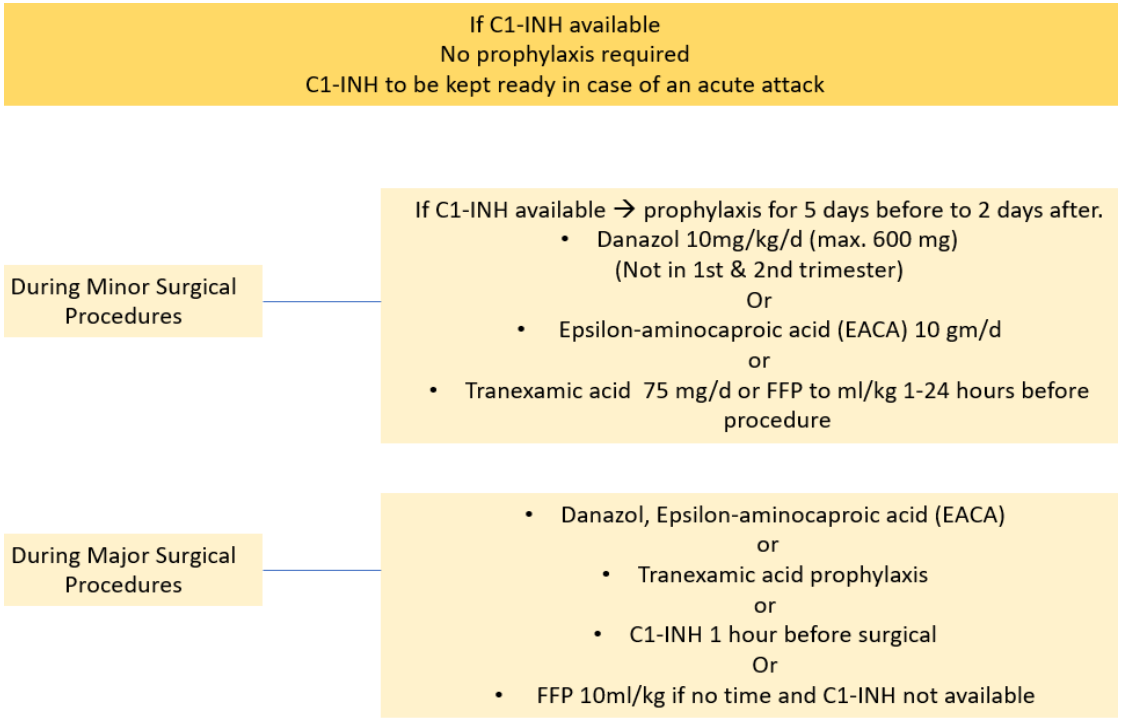

Figure 7. Short Term Prophylaxis During Surgical Procedures.

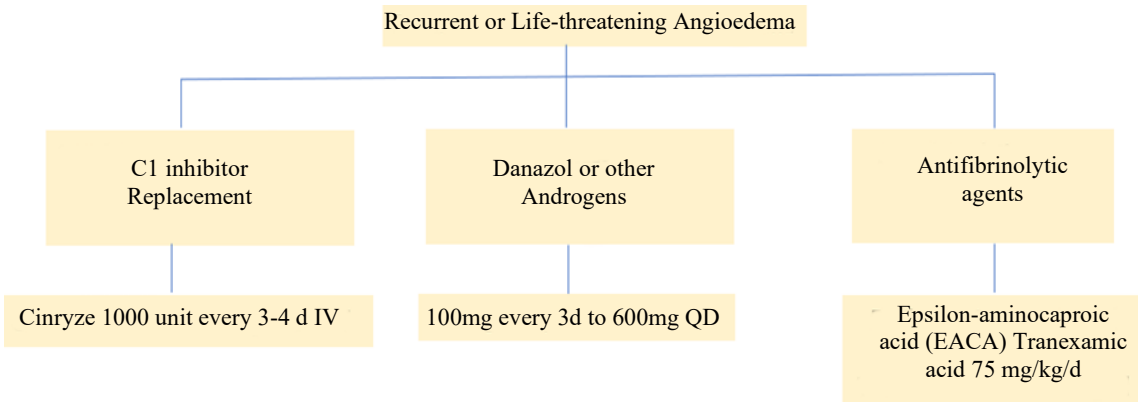

Figure 8. Long-term prophylaxis of hereditary angioedema.

Long-term prophylaxis is contemplated for specific cases where the condition is progressively severe, marked by moderate to severe episodes of laryngeal edema or significant hindrance in daily activities. Androgens such as Danazol or Stanozolol are initiated at higher doses (400-600 mg per day) and gradually reduced to the minimum effective dosage (50-200 mg, twice a week), with regular monitoring of liver function tests and lipid profile. Side effects of danazol include headache, weight gain, liver dysfunction, hirsutism, and menstrual disturbances [35-38]. If dose of danazol> 200 mg/day, monitor complete blood count, liver function test, creatinine kinase, lactic dehydrogenase, fasting lipid profile, and urinalysis at baseline and q6mo. Abdominal ultrasound to be performed annually or every six months. Danazol is not to be used in children, during first 2 trimesters of pregnancy, during lactation, and in patients with hepatitis or cancer. If patient cannot tolerate attenuated androgens, antifibrinolytic agents (plasmin inhibitors), such as tranexamic acid, 25-50 mg/kg/d divided twice or thrice a day (3-6 gm per day maximum) or e-aminocaproic acid could be used. They are less effective than attenuated androgens.

Management of suspected idiopathic Histaminergic-Angioedema

The diagnosis of idiopathic histaminergic angioedema can be established by a meticulous medical history, by excluding other disorders associated with AE of known etiology and by ascertaining the failure of conventional antihistamine therapy. The proposed algorithm for management given in (Figure 9).

Management of Acquired angioedema (AAE)

Acquired angioedema (AAE) arises from an elevated breakdown of C1-INH that surpasses the body's ability to produce it. It is often observed in older individuals without a family history and is commonly linked with lymphoproliferative disorders like B cell lymphoma, neoplastic conditions, autoimmune diseases, and connective tissue disorders such as systemic lupus erythematosus (SLE), or infectious diseases. AAE is further categorized into two subtypes: Type I and Type II. Type I results from increased consumption of C1-INH, frequently found in patients with rheumatologic disorders and B cell lymphoproliferative diseases. These patients produce anti-idiotypic antibodies against B cell immunoglobulins.

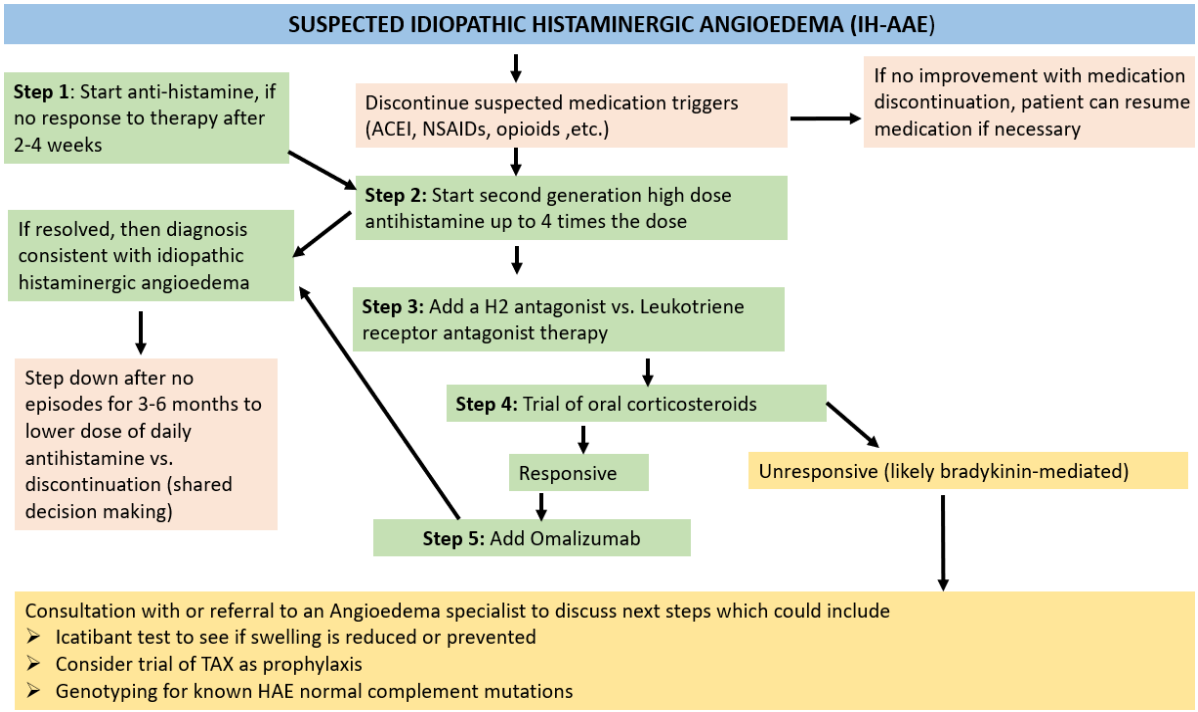

Figure 9. Management of suspected idiopathic histaminergic-angioedema.

On the other hand, Type II AAE stems from autoantibodies, specifically Immunoglobulin G, which target and neutralize C1-INH. AAE patients need higher doses of plasma derived C1-inhibitor or become progressively non-responsive to it. During an emergency, plasm -derived C1-inhibitor or additionally Icatibant or Ecallantide are used in management of AAE [36,37]. For the prophylactic management of acquired angioedema (AAE), prolonged treatment with anti-fibrinolytics has shown greater effectiveness compared to attenuated androgens. Additionally, C1-INH may also be administered for long-term prevention in specific patients.

CONCLUSION

In clinical settings, distinguishing between angioedema mediated by histamine (AE-H) and angioedema mediated by bradykinin (AE-BK) poses challenges. AE-H can be managed with epinephrine injections, antihistamines, and oral corticosteroids. If these treatments yield no response, AE-BK should be considered. While the classification of angioedema without wheals into three main types (AE-H, AE-BK, and AE-UNK) is widely accepted, there is a lack of consensus, particularly in types like AE-UNK / InH-AAE, needs further clarification and definition. Future efforts should prioritize to increase awareness of all angioedema types and developing simpler diagnostic approaches. In certain cases, the future of managing angioedema may involve genetic profiling to tailor therapy for improved safety and effectiveness which may arrest its progression.

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