Practice Parameter: Algorithmic Management of Recurrent Angioedema

Indian Academy of Pediatrics – Allergy and Applied Immunology Chapter
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Introduction

Angioedema is defined as "a paroxysmal, localized, and self-limiting swelling of the subcutaneous and/or submucosal tissue, due to a temporary increase in vascular permeability." (DANCE Classification, 2024).

Angioedema is characterized by swelling in the deeper layers of the dermis and subcutaneous tissue due to fluid accumulation while urticaria typically affects only the superficial skin layers. Most common sites of angioedema include face, lips, eyes, hands, feet, genitalia, larynx, and gastrointestinal tract. The overlying skin in the affected areas usually remains normal in color, though it may look erythematous. Angioedema episodes are generally painless and lack associated itching, though some individuals may experience pain or a burning sensation. Recurrent episodes impact quality of life significantly and require careful evaluation and management.

I Differential diagnosis of angioedema based on anatomical location.

TABLE 1

Location	Angioedema mimicker	Differentiating points
Lips	Oro Facial Granulomatosis	Initial painless Intermittent swelling, non-caseating granulomas on histology
	Melkersson-Rosenthal Syndrome	Triad of orofacial oedema, facial palsy, fissured tongue
Limb	Cellulitis	Painful erythema, fever, raised inflammatory markers
	Lymphoedema	Excessive interstitial lymphatic fluid retention due to impaired drainage.

	Thrombosis	Painful swelling
Periorbital tissues	Orbital cellulitis	Painful swelling, fever headache
	Thyroid eye disease	Chemosis, exophthalmos, abnormal thyroid tests
	Dermatomyositis	Arthralgia/arthritis, myositis, dysphagia, lung fibrosis, Gottron's papules Raynaud's phenomenon on examination
	Sjogren syndrome	Dry eyes, dry mouth, arthralgia/arthritis, parotid gland swelling. ANA abs present
	Lymphoma	Constitutional symptoms, consistent Immuno phenotyping /Flow cytometry report
	Superior vena cava syndrome	Diffuse engorgement of face and neck. Pemberton's sign positive
Epiglottis/ Uvula	Epiglottitis	Fever and exudates on swab
Genitalia	Testicular torsion	Acute and painful testicular swelling
Systemic	filariasis	Painful when chronic, blood film for microfilarae, filarial IgG EIA
	Contact dermatitis	Crucial history of culprit exposure and specific occupation
	Atopic dermatitis	Persistent symptoms rather than episodic symptoms, characteristic rash morphology and distribution, involvement of superficial skin layers, erythema, itching.

	Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome	Specific drug exposure history followed by extensive rash, fever and organ involvement, lymphadenopathy, eosinophilia and atypical lymphocytosis
	Nephrotic syndrome	Generalized edema, proteinuria, hypo albuminemia, foamy urine

The first step into angioedema management approach is to identify the type of angioedema. The most recent DANCE classification classifies angioedema into 5 categories: AE-MC (Mast Cells), AE-BK (Bradykinin), AE-VE (vascular endothelium), AE-DI (Drug induced) AE-UNK (unknown mechanisms). The 2 most common forms of angioedema in clinical practice are:

1) Mast cell mediator mediated

2) Bradykinin-mediated

It is important to differentiate the 2 conditions clinically because the diagnostic evaluation and the management protocols are different in these 2 groups.

Table 2 enumerates the points to differentiate between the 2 groups.

TABLE 2

Angioedema Type	Mast cell mediator mediated angioedema	Bradykinin mediated angioedema
Age of presentation	Any age	Variable depending on the subtype. Most patients with hereditary angioedema have onset before the age of 20 years.
Onset of swelling	Few minutes to 4 hours.	Slowly over few hours (usually 12-24 hours)
Duration of episode	Usually less than 24 hours	Almost always more than 36 to 48 hours
Urticaria/wheals	Common	Rare
Pruritus	Common	Rare, may be a prodromal symptom in few.
Site of angioedema	Predominantly facial	Can affect face, hands, feet, tongue, genitalia and larynx Gastrointestinal symptoms are common
Prodromal symptoms	Rare	Common
Triggers	Uncommon. food, insect bites or stings, medications, environmental allergens,	Stress, mechanical trauma, hormonal effects (puberty, menstruation, or pregnancy), medication, infections, other accompanying diseases, or surgical interventions

	physical stimulus, and infection. Drugs like NSAIDs, Beta lactam	
Response to antihistamines and/or corticosteroids	Yes	No
Family history	Rare	Family history is characteristic; autosomal dominant transmission (80-85% cases)

II Pathophysiology of Angioedema

Most patients with mast cell mediator mediated angioedema have no underlying etiology. Common triggers for mast cell mediator mediated angioedema include foods, drugs, stinging insects, venoms, including fire ants. The most common implicated food allergens include milk, egg, shellfish, peanuts, and tree nuts. Unless there is definite history of a specific food trigger, routine skin prick testing is not recommended. True food allergy should be differentiated from oral allergy syndrome, which is mild mouth, tongue, pharyngeal swelling. Beta-lactam antibiotics and NSAIDs are the most identified drug triggers of angioedema. Other drugs, such as perioperative anesthetic agents, radioactive dyes should be considered for patients undergoing chemotherapy or having a history of surgery.

Bradykinin mediated angioedema comprises of hereditary angioedema and acquired angioedema. Angiotensin converting enzyme inhibitor (ACEI) induced angioedema may also be bradykinin mediated.

III Evaluation a patient with angioedema

If angioedema is the part of systemic anaphylaxis, it should be managed as per anaphylaxis protocol. Once the patient is stabilized, a thorough history should be obtained (figure 1). This includes details about, onset of swelling, duration of swelling, location, exposure to potential triggers, physical signs and symptoms, past history of wheals, or wheals concomitant with the angioedema, drug history and family history of angioedema. In addition to food or medications triggers, chronic infection, thyroid disorders, autoimmune diseases, malignancy and physical triggers (i.e. pressure, exercise, and vibration) must also be ruled out. This information is essential for distinguishing between various forms of angioedema as the diagnosis of angioedema is essentially clinical and involves good history taking and assessing the triggers.

In mast cell mediator mediated angioedema, no laboratory investigations are required in the initial episode as the diagnosis is exclusively clinical. Laboratory investigations help only if a patient is not responding to an adequate dose of antihistamine given for 6 weeks. It helps in

understanding the auto-allergic and autoimmune nature of mast cell mediator mediated angioedema.

Tests that need to be done in a patient who fails to respond to 6 weeks of an adequate dose of antihistamine are complete blood count, C reactive protein, differential leukocyte count, absolute eosinophil count, absolute basophil count, serum TSH levels and anti TPO antibodies.

Diagnosis of bradykinin mediated Angioedema (BK-AE) needs laboratory investigations to confirm the diagnosis. C4 and C1-inhibitor levels are diagnostic in most cases of bradykinin mediated angioedema. Hereditary Angioedema type 1 (HAE-C1INH Type 1) will have low C4 and low C1-INH levels while hereditary angioedema type 2 (HAE-C1INH type 2) will have low C4 and normal/high C1-INH levels. Patients with acquired angioedema have low C4 and low C1INH levels. C1q levels are low in 60-70% patients with acquired angioedema while they are normal in HAE.
Normal C1-INH HAE is extremely rare and is usually diagnosed with the help of genetic test.

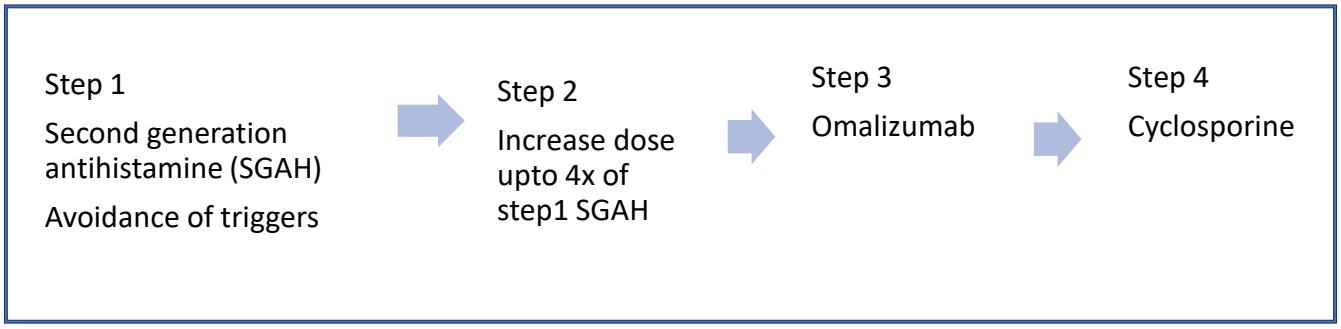
TABLE 3

	HAE Type 1	HAE Type 2	C1-INH-AAE	ACEI-AE
Time of presentation	Usually below the age of 20	Usually below the age of 20	4^{th} -5^{th} decade of life	4^{th} -5^{th} decade of life
C4 Levels	Low	Low	Low	Normal
C1-INH Antigenic Concentration	Low	Normal or increased	Normal or low	Normal
C1-INH Functional Activity	Low (<50 %)	Low (<50 %)	Low (<50 %)	Normal
C1q Levels	Normal	Normal	Low (70 %)	
Anti-C1-INH Antibodies	Not typically present	Not typically present	detected in 50 % (IgG, IgM, IgA)	
Mutation	*SERPING1* (90 %)	*SERPING1* (90 %)	None	None

IV Management of angioedema

Treatment of chronic mast cell mediated angioedema largely follows the guidelines of chronic urticaria. It involves starting a second-generation antihistamine (cetirizine, levocetirizine, fexofenadine, loratadine etc.) and escalating dose up to 2 to 4 times over few weeks. Some Severe refractory cases may require omalizumab or cyclosporine (table 4).

TABLE 4



Management of Hereditary Angioedema

One must avoid ACE inhibitors and estrogens in all patients with HAE.

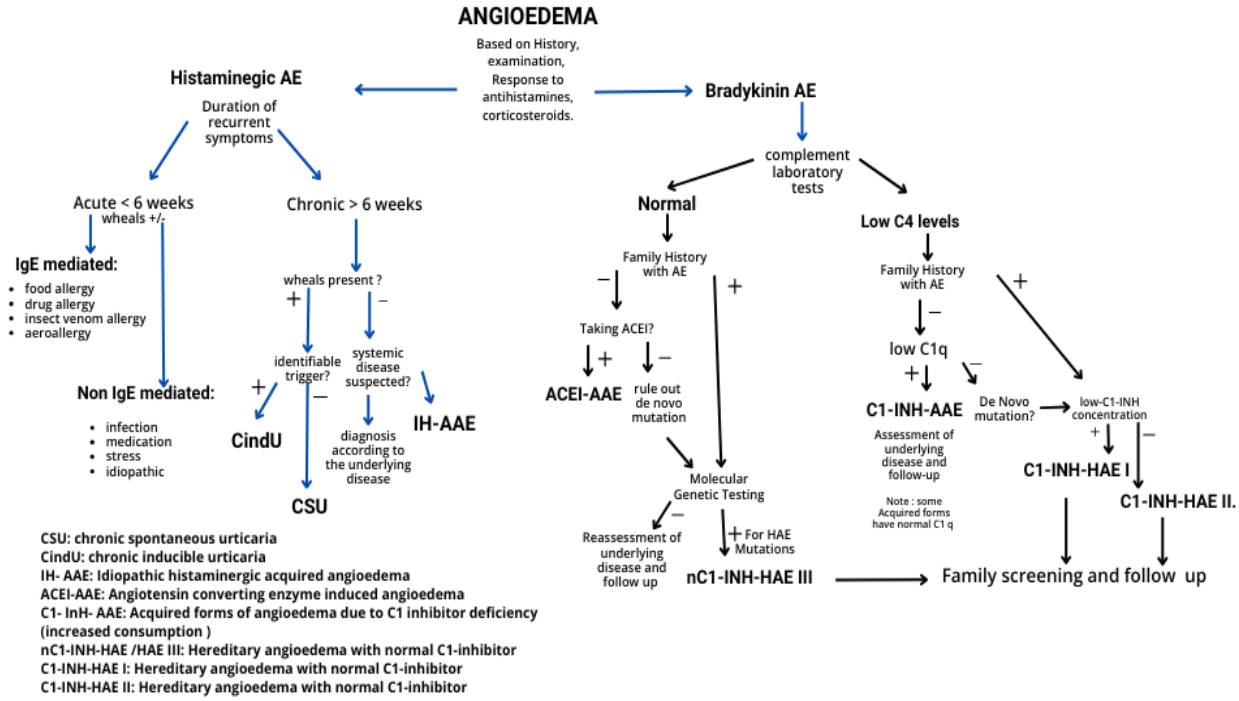
Acute attacks (On demand treatment): Plasma derived C1-inhibitor is the drug of choice for management during acute episodes. It is to be used in a dose of 10-20 unit per Kg body weight and injected intravenously. The dose may be repeated after 2 hours if there is no response. Fresh frozen plasma may be used if plasma derived C1-inhibitor concentrate is not available. However, fresh frozen plasma is not as effective as plasma derived C1-inhibitor concentrate, is slow to act and has potential side effects.

Long term prophylaxis is used for patients who have at least one episode of angioedema every month or who have life-threatening episodes. Tranexamic acid and/or attenuated androgens are commonly used drugs for long-term prophylaxis. Plasma derived C1-inhibitor concentrate is also used for long-term prophylaxis especially in situations such as during pregnancy, breast feeding and for young children.

Short-term prophylaxis: Plasma derived c1-inhibitor concentrate is the drug of choice for short term prophylaxis before dental and surgical procedures.

For ACE inhibitor induced angioedema – Angiotensin receptor blocker can be safely sued.

Figure 1



Suggested Reading

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