HKU Med
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Department of Medicine
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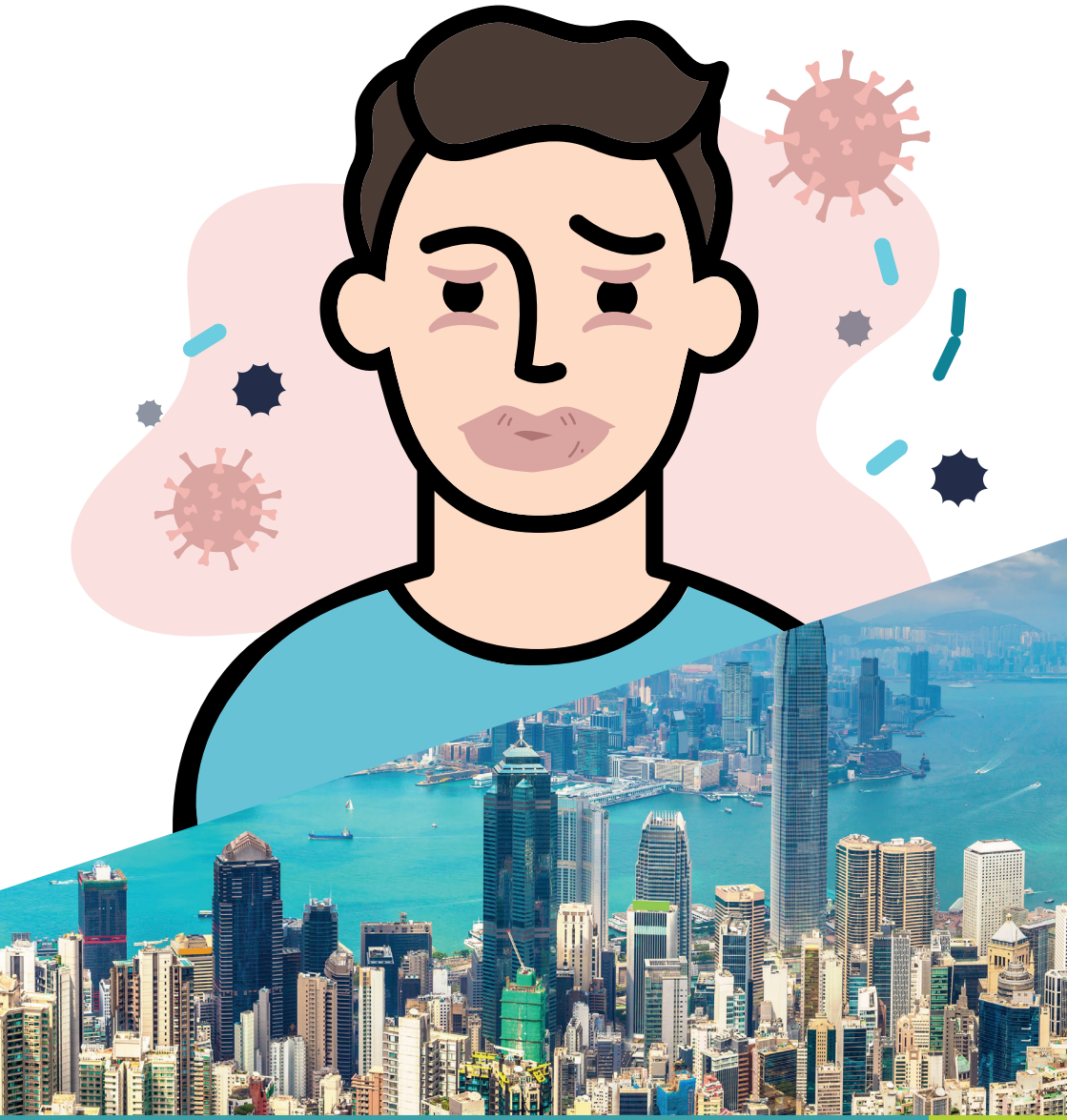
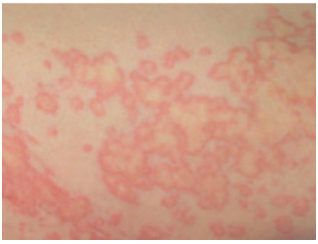
Approach to Angioedema in Hong Kong



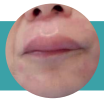
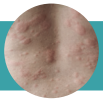
What is urticaria?

Urticaria is characterized by the presence of wheals (hives), angioedema, or both.[1]



What is the difference between angioedema and wheals (hives)?

The differences between wheals and angioedema can be highlighted in the table below.[1,3]

Features	 Angioedema	 Wheals (hives)
Tissues involved	Subcutaneous and submucosal layer	Epidermis and dermis
Areas involved	Skin and mucosa	Skin only
Symptoms	Pruritus may or may not be present. Swelling, can be with pain and tenderness	Pruritus is usually present. Pain and tenderness is uncommon.
Physical signs	Skin coloured swelling below the skin / mucosa	Erythematous “wheals and hives”
Time for resolution of symptoms	Long (can take up to 72 hours)	Short (usually within 24 hours)

What are the two main types of angioedema?

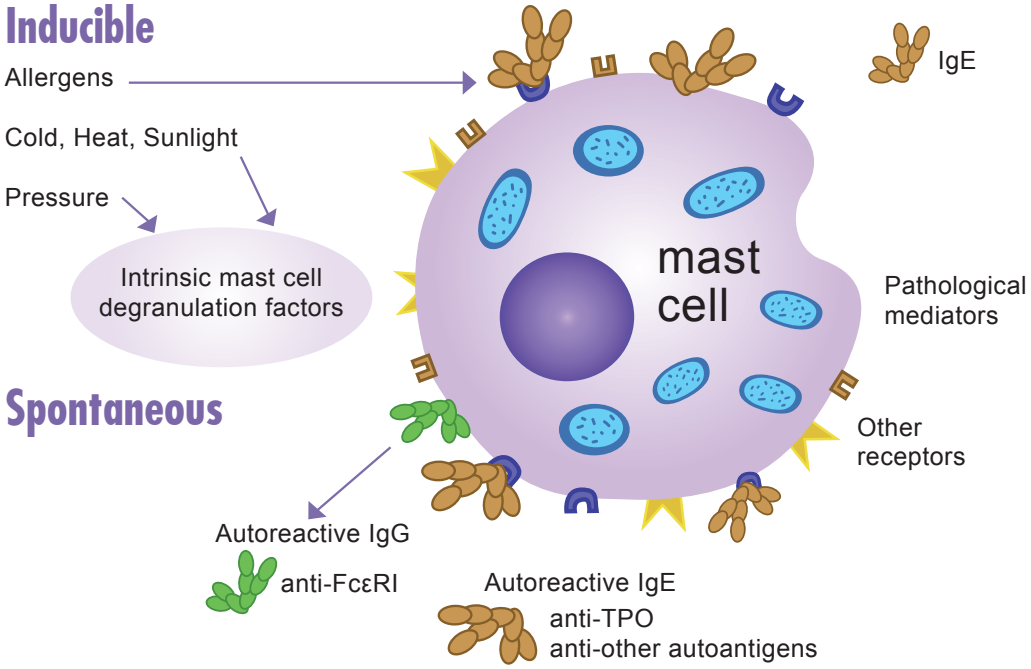
Angioedema can be broadly classified into 2 types:[4]

1. **Histamine-mediated** angioedema (much more common)
2. **Bradykinin-mediated** angioedema

What is the pathogenesis underlying angioedema?

In **histaminergic angioedema**, angioedema occurs as a result of mast cell degranulation elicited by an allergic reaction to drugs, food, venom, etc., leading to a release of derived mediators that cause vasodilation and increased vascular permeability.[5] Other known causes include acute urticaria and chronic spontaneous or inducible urticarias.[2]

In a patient with histaminergic urticaria



Bradykinergic angioedema results from excessive bradykinin levels, which leads to increase in vascular permeability. Below are some possible ways:[4]

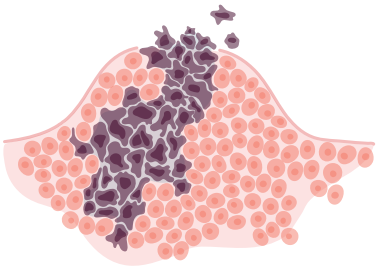
1. Use of **certain drugs** such as angiotensin converting enzyme inhibitors (ACE - inhibitors), which inhibit bradykinin degradation into its inactive form.

2. **Hereditary angioedema** (HAE), a rare autosomal dominant condition presenting with a deficiency of C1-esterase inhibitor (C1-INH) which leads to increased bradykinin production.

3. **Acquired angioedema:** resulting from autoantibodies formed against C1-INH.

Can angioedema signify malignancy?

Some cases of bradykinergic angioedema are caused by an acquired C1-INH deficiency. This may be associated with malignancies including lymphoproliferative disorders and monoclonal gammopathies. Adenocarcinomas have also been implicated.[7] Therefore, especially in older patients with C1-INH deficiency, one needs to consider and exclude potential malignancy with individualized and age-appropriate cancer screening.



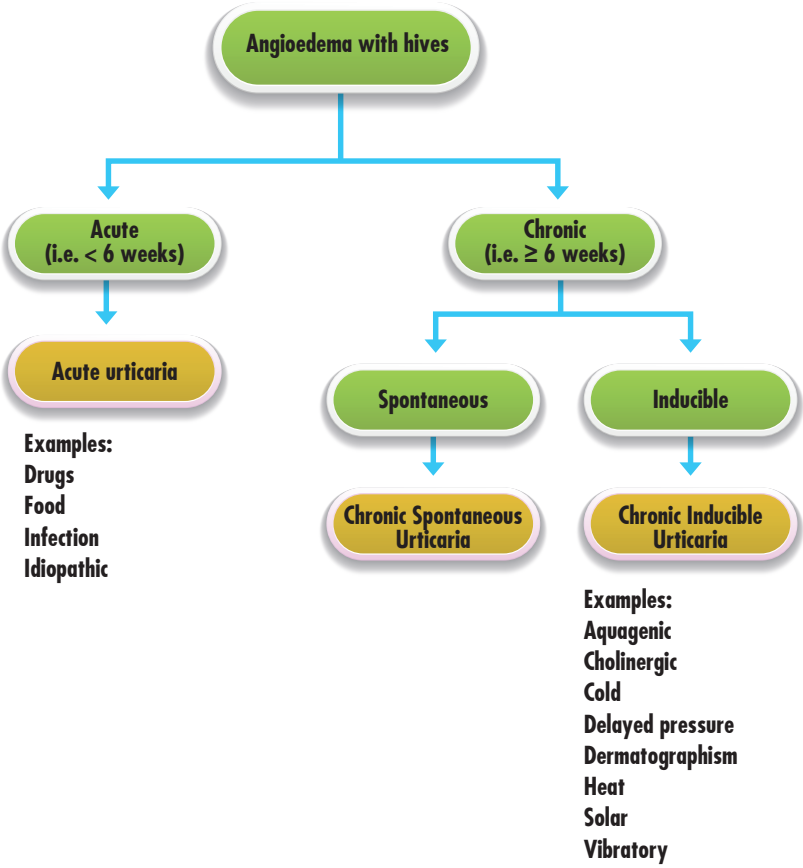
How to clinically differentiate histaminergic and bradykinergic angioedema?

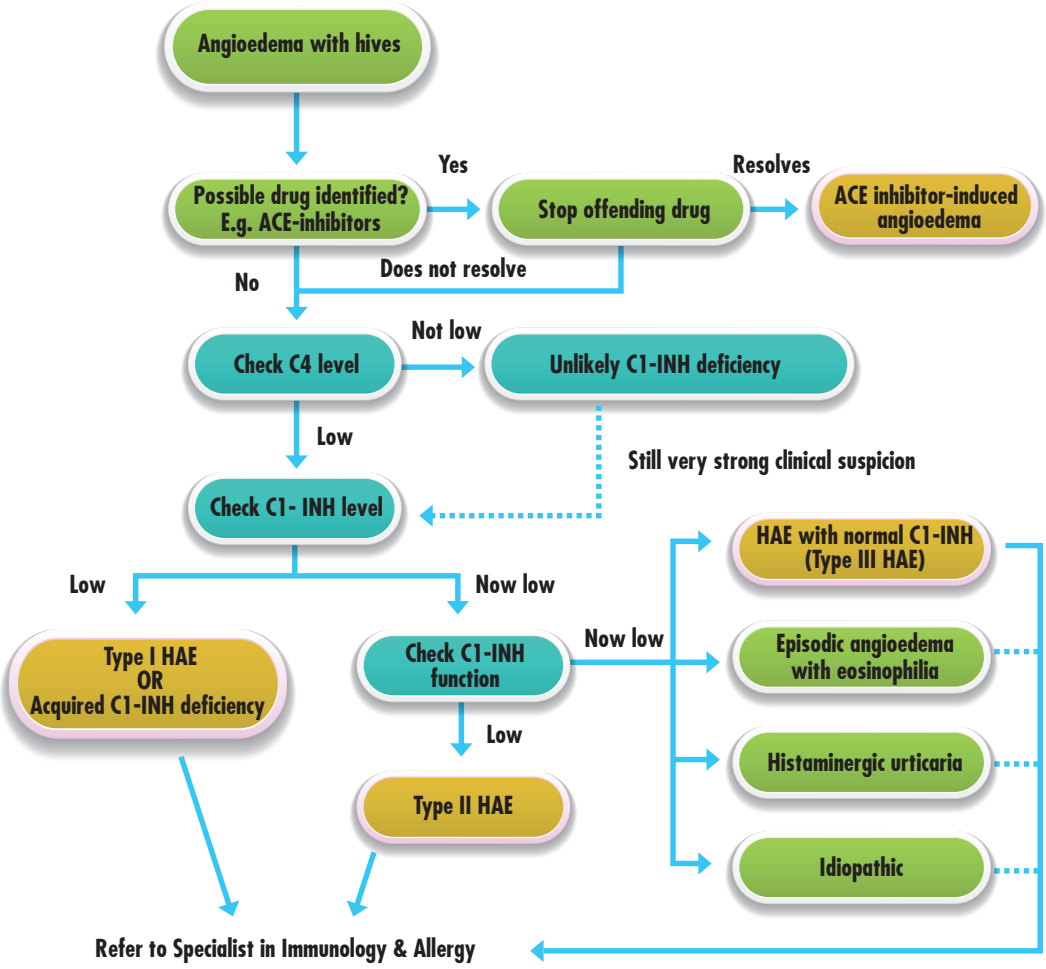
Clinical differences between histaminergic and bradykinergic angioedema can be illustrated in the table below.[3,4]

Features	Histaminergic	Bradykinergic
Concomitant hives?	Yes, although not always	No
Any gastrointestinal involvement?	Uncommon, possible in cases of anaphylaxis	Yes, bowel edema can commonly present with gastrointestinal upset. In severe cases, can lead to bowel obstruction and ischaemia.
Any respiratory involvement?	Uncommon, but possible in cases of anaphylaxis	Possible, due to laryngeal oedema
Duration of symptoms	Shorter, usually subside within 1-3 days	Longer, can last for 3-4 days
Response to antihistamines, steroids or adrenaline	Yes	No
Response to bradykinin inhibitors or C1-INH replacement	No	Yes

What is the general diagnostic approach to angioedema?

The general approach to angioedema is highlighted in the flowchart below.




Angioedema with hives
Possible drug identified? E.g. ACE-inhibitors
Yes
Stop offending drug
Resolves
ACE inhibitor-induced angioedema
No
Does not resolve
Check C4 level
Not low
Unlikely C1-INH deficiency
Low
Still very strong clinical suspicion
Check C1- INH level
Low
Now low
Type I HAE OR Acquired C1-INH deficiency
Check C1-INH function
Now low
Low
Type II HAE
HAE with normal C1-INH (Type III HAE)
Episodic angioedema with eosinophilia
Histaminergic urticaria
Idiopathic
Refer to Specialist in Immunology & Allergy

Histaminergic angioedema

History taking is crucial in distinguishing the underlying etiology of angioedema. The **presence of hives is probably the most useful differentiating symptom and points towards histamine-mediated angioedema.**[8]

Patients who develop hives within one hour of exposure to a suspicious allergen should be assessed for possible IgE-mediated allergic reaction. These are characterized by immediate, consistent and reproducible symptoms to a specific allergen exposure, such as to a specific food, drugs, or insect bites.[8]

specific food | drugs | insect bites

They may also volunteer a history of anaphylaxis or evidence of multi-system involvement.

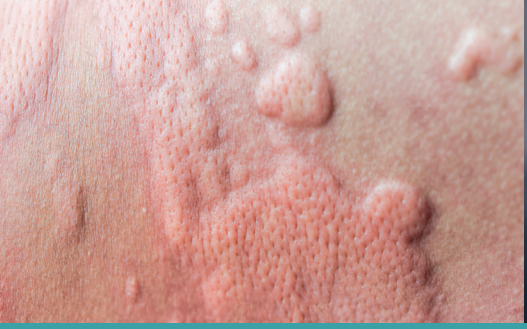
Chronic urticaria with angioedema do not usually present with anaphylaxis. There is often no identifiable culprit. These hives can occur spontaneously or in response to a variety of physical triggers. They usually respond rapidly to antihistamines.[8]

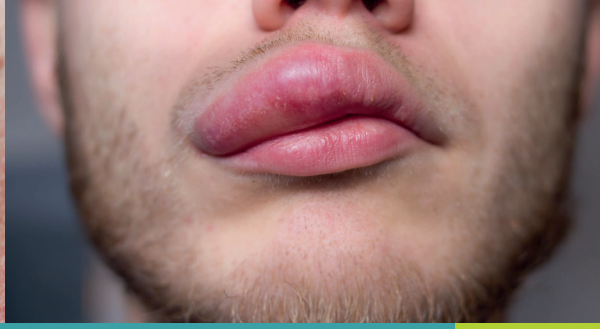
Bradykinergic angioedema

Angioedema **without hives, especially with features suggestive of bradykinergic angioedema**, should prompt physicians to carefully look at the drug history.[8]

Patients with bradykinergic angioedema should avoid ACE-inhibitors, regardless of the cause. If the patient is on ACE-inhibitors, one should stop the drug and re-evaluate for persistent symptoms of angioedema.

If there is no obvious drug-related cause, a C4 level +/- C1-INH level or function should be taken to rule out C1-INH deficiency. A low C1-INH level or function maybe indicative of HAE or acquired C1-INH deficiency.[4]

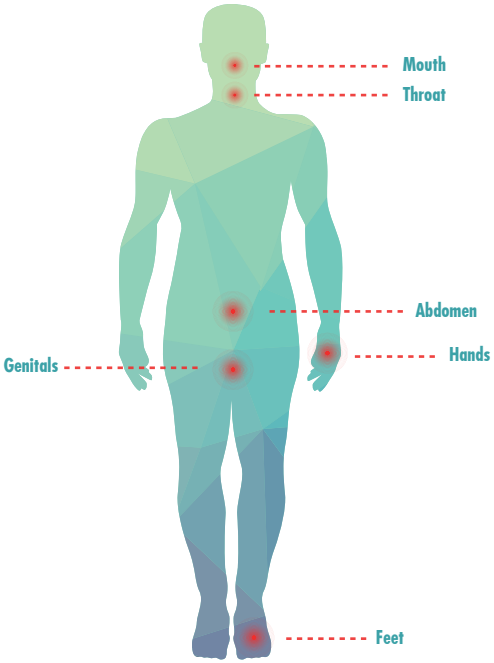




Are there any useful diagnostic tests?

Histaminergic-mediated angioedema is usually diagnosed by detailed history taking to identify possible allergic reactions.[8] We do not recommend routine "screening" with specific IgE or skin tests unless the history is suggestive of possible allergy.[6] Uncertain cases should be referred to a Specialist in Immunology & Allergy for further workup. Routine blood taking for autoimmune markers are generally not recommended for cases of urticaria.[2]

C4 and C1-INH levels should only be taken if the patient presents with a history suggestive of bradykinin-mediated angioedema. **Taking a C1-INH level in cases of histaminergic angioedema is not useful and results in unnecessary patient anxiety and referrals.** Genetic testing, C1-INH function and C1q levels should only be ordered by an immunologist.



What is the treatment for angioedema?

Allergies should be managed as per standard care by strict avoidance of the offending culprit.[2]

Patients with chronic spontaneous urticaria, by definition, are not triggered by allergens. However, some patients may find that NSAIDs may worsen symptoms. Treatments for chronic spontaneous urticaria include use of second generation anti-histamines, anti-IgE therapy and other immunosuppressants.[2]

Further information regarding management and subsequent follow-up can be found in our Chronic Spontaneous Urticaria booklet available at http://imm.hku.hk/.

http://imm.hku.hk/

When should the patient be referred to immunologist for angioedema?

Patients with refractory urticaria, not responsive to regular second generation anti-histamines should be referred to a Specialist in Immunology & Allergy assessment and management.[2] All cases of suspected or confirmed HAE should also be promptly referred for specialist care.[9]

HEREDITARY ANGIOEDEMA HAE IN HONG KONG

Although this is a rare hereditary condition, physicians should be aware of this disease entity because prompt diagnosis and treatment can be lifesaving.

What should prompt workup for HAE?

Unexplained isolated angioedema without hives, in the absence of an offending drug, should prompt workup for HAE or acquired angioedema. A family history of recurrent angioedema should further raise suspicion. Patients with HAE usually present between childhood and young adulthood.[10]

Unexplained, isolated angioedema without hives should prompt workup for HAE or acquired angioedema

However, in Hong Kong, initial symptom onset has ranged from infancy to elderly. Early diagnosis reduces hospitalizations, unnecessary interventions such as surgeries, and mortality rates. It can also result in earlier family screening and better family planning for future generations.[10,11]

What can be done during an angioedema attack for patients with HAE?

In Hong Kong, patients confirmed with HAE should have regular follow-up with their immunologist and alerted in their electronic medical records. Several international guidelines have outlined the treatment of HAE.[9,11,12]

These episodes of angioedema ***do not*** respond to antihistamines, steroids, nor adrenaline,[10] and these patients should not be managed per standard anaphylaxis protocols. We ***do not*** recommend delaying treatment.[12] Early evaluation by a Specialist in Immunology & Allergy is preferred.[9]

Icatibant (a bradykinin receptor antagonist) has been approved for use in Hong Kong.[13] C1-INH replacement therapy is also available for selected patients.[10]

Patients with acute medication on-hand (either C1-INH replacement therapy or icatibant) should also have an individualized emergency treatment plan and alert card outlining the use of medications during attacks.[14] We strongly recommend healthcare providers to be prepared to recognize and treat these reactions properly with prompt delivery of C1-INH or icatibant.

Are there any precautions that we need to consider in patients with HAE?

Drugs such as ACE-inhibitors and estrogen containing compounds should be avoided in all patients with HAE.[10]

Surgeries and dental procedures can trigger angioedema attacks of unpredictable severity in patients with HAE.[10] Patients should be evaluated on a case-by-case basis to decide whether hospital admission for close observation or prophylactic medications are required. Close communication between patients, surgeons, anaesthetists, and a specialist in immunology and allergy is crucial.

The Hong Kong HAE Patient Group

The Hong Kong HAE Patient Group was formed in 2019 to support patients with hereditary angioedema and their families to create awareness, provide education, and gain access to modern treatments so that HAE patients can enjoy a higher quality of life. For more information, please visit https://haehk.haei.org/

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https://haehk.haei.org/

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