**Introduction**

1. Angioedema is characterized by localized swelling in the deeper layers of the skin and mucous membranes due to leakage of fluid from blood vessels into the surrounding tissue. It can be classified into different types, with the two main categories being hereditary angioedema (HAE) and angiotensin-converting enzyme (ACE) inhibitor-induced angioedema.
2. HAE is a rare genetic disorder caused by C1 esterase inhibitor (C1-INH) deficiency or dysfunction, resulting in uncontrolled activation of inflammatory pathways including the kallikrein-kinin system. It is characterized by recurrent, unpredictable episodes of angioedema without urticaria, which can be disfiguring and painful. Most importantly, angioedema affecting the upper airway can obstruct breathing and lead to asphyxiation.
3. ACE inhibitor-induced angioedema is caused by increased levels of bradykinin due to reduced catabolism from ACE inhibitor use. While generally less severe than HAE episodes, ACE inhibitor-induced angioedema can also result in life-threatening upper airway obstruction.
4. Distinguishing between HAE and ACE inhibitor-induced angioedema is crucial, as management strategies differ significantly between the two conditions. For emergency medicine clinicians, a high index of suspicion, prompt recognition of attacks, and appropriate treatment are essential to optimize patient outcomes.
5. Recent therapeutic advancements for HAE include C1-INH replacement therapy, kallikrein inhibitors, and bradykinin receptor antagonists. For ACE inhibitor-induced angioedema, little high-quality evidence exists supporting pharmacotherapies beyond ACE inhibitor discontinuation and supportive care.

**Epidemiology**

1. Hereditary Angioedema
   1. Prevalence: 1 in 10,000 to 1 in 50,000 individuals
   2. No gender predisposition
   3. Family history often present
   4. Three inheritance patterns: autosomal dominant, autosomal recessive, de novo mutations
2. ACE Inhibitor-Induced Angioedema
   1. Incidence: 0.1-0.7% of patients on ACE inhibitors
   2. Higher risk populations:
      1. Female sex
      2. African American race
      3. History of smoking
      4. Concomitant use of dipeptidyl peptidase-4 (DPP4) inhibitors
3. Key Epidemiological Considerations
   1. HAE less common than ACE inhibitor-induced angioedema
   2. Low baseline prevalence of HAE necessitates high index of suspicion
   3. ACE inhibitor-induced angioedema can occur anytime during therapy, even after many years
   4. Certain populations at higher risk for ACE inhibitor-induced angioedema

**Pathophysiology**

I. Hereditary Angioedema

A. C1 Inhibitor Deficiency

* C1 inhibitor (C1-INH) inhibits proteases of the complement, coagulation, fibrinolytic and kinin pathways
* Mutations in the SERPING1 gene encoding C1-INH lead to deficiency

B. Unregulated Bradykinin Activity

* Insufficient C1-INH activity results in uncontrolled kallikrein-kinin system
* Plasma kallikrein cleaves high-molecular-weight kininogen into bradykinin
* Excessive bradykinin increases vascular permeability and causes angioedema

C. Types of HAE

1. Type I (~85% of cases)

* Reduced C1-INH levels (5-30% of normal)
* Autosomal dominant inheritance

1. Type II (~15% of cases)

* Normal C1-INH levels but reduced function
* Autosomal dominant inheritance

1. Type III (rare)

* Normal C1-INH levels and function
* Unknown genetic mutation; potential role of other mediators like bradykinin

II. ACE Inhibitor-Induced Angioedema

A. Impact of ACE Inhibitors

* ACE inhibitors inhibit conversion of angiotensin I to angiotensin II
* This indirectly reduces catabolism of bradykinin
* Bradykinin accumulates and directly triggers angioedema

B. Risk Factors

* Female gender, African American race, smoking history, DPP4 inhibitor use
* Polymorphisms in genes encoding ACE and aminopeptidase P enzymes

C. Timing of Onset

* Highest risk in first week after initiating ACE inhibitor
* Can occur anytime, even after many years of uneventful ACE inhibitor use

In summary, both HAE and ACE inhibitor-induced angioedema stem from excess unpredictable bradykinin activity causing increased vascular permeability and fluid extravasation into soft tissues. However, distinct genetic or pharmacological triggers mediate this process in each condition.

**Clinical Manifestations**

I. Hereditary Angioedema

A. Attack Frequency and Severity

* Recurrent, self-limiting episodes of angioedema without urticaria
* Frequency ranges from weekly attacks to once a year
* 30-50% of patients report prior ICU admission or intubation

B. Location of Swelling

* Extremities (hands, feet), face, mouth, tongue, throat, gastrointestinal tract, genitalia
* Upper airway: potentially life-threatening asphyxiation risk

C. Attack Characteristics

* Non-pruritic, non-painful swelling
* Gradually progresses over 12-36 hours, lasts 48-120 hours
* Resolves spontaneously but slowly without treatment

D. Triggers for Attacks

* Trauma, medical/dental procedures
* Stress, infections, menstruation, estrogen medications
* Rarely ACE inhibitors

II. ACE Inhibitor-Induced Angioedema

A. Onset and Location

* Sudden onset within hours of ACE inhibitor exposure
* Face, lips, tongue, oropharynx most commonly affected

B. Attack Characteristics

* Non-pruritic, non-erythematous localized swelling
* Peak intensity within 24 hours of onset
* Resolves over 1-5 days after stopping ACE inhibitor

C. Timing and Triggers

* Highest risk in first week after ACE inhibitor initiation
* Can occur anytime, even after years of uneventful use
* Guaranteed recurrence with re-exposure to ACE inhibitor

**Diagnosis**

I. Hereditary Angioedema

A. Medical History

* Lifelong history of recurrent angioedema without urticaria
* Family history may provide clue to diagnosis

B. Physical Exam During Attack

* Non-pitting edema of the skin or mucosal tissues
* No urticaria, pruritus, or erythema

C. Initial Laboratory Testing

* CBC, metabolic panel to rule out alternative causes
* Serum tryptase level during attack

D. Confirmatory Laboratory Testing

1. C4 Levels: Low due to uncontrolled complement activation
2. C1-INH Antigenic Levels and Function: Reduced levels and function
3. Genetic Testing: Identify causative SERPING1 mutations

II. ACE Inhibitor-Induced Angioedema

A. Medical History

* Detailed medication history: onset related to ACE inhibitor exposure
* No prior history of angioedema

B. Physical Exam

* Non-pitting edema without urticaria/pruritus

C. Initial Laboratory Testing

* CBC, basic metabolic panel to exclude other etiologies
* No specific confirmatory laboratory tests

D. Diagnosis

* Based on history of ACE inhibitor use with temporal relationship
* Exclusion of alternative diagnoses

**Management - Overview**

* For angioedema, securing the airway is the top priority for laryngeal/pharyngeal swelling. Antihistamines are appropriate for urticarial angioedema, while bradykinin-targeted therapies are needed for hereditary and ACE inhibitor-induced angioedema.
* Overall management hinges on differentiating the type of reaction and providing the appropriate pharmacotherapy based on the underlying pathophysiology. An individualized approach optimizes patient outcomes.

**Pharmacotherapy for Angioedema**

Initial Priorities in Angioedema Presentations:

* Assess airway patency. Secure airway in impending obstruction.
* Discontinue any potential triggering medications.
* Provide supplemental oxygenation and IV fluid resuscitation as needed.
* Differentiate histaminergic vs non-histaminergic forms.

**Histaminergic Angioedema with Urticaria:**

First-line:

Antihistamines:

* H1-blockers (diphenhydramine, cetirizine, loratadine, etc.)
* H2-blockers (ranitidine, famotidine, cimetidine)
* Use high-end doses up to 4-fold conventional doses
* Block histamine-induced vasodilation and pruritus
* Onset: 30-60 minutes, peak: 1-2 hours

Corticosteroids (prednisone, methylprednisolone):

* Modulate inflammatory response
* Help prevent recurrent angioedema
* No proven benefit acutely
* Onset: 4-6 hours

Epinephrine:

* Reserved for laryngeal involvement or anaphylaxis
* 0.3-0.5 mg IM thigh in adults, 0.01 mg/kg IM in children

**Non-Histaminergic Angioedema:**

**Hereditary Angioedema:**

C1-INH Concentrates:

* Berinert (20 units/kg IV), Ruconest (50 units/kg IV), Cinryze (1000 units IV)
* Replace deficient or dysfunctional C1-INH
* Reverses bradykinin-mediated increased vascular permeability
* Onset: 0.5-2 hours, duration up to 4 days
* Adverse effects: hypersensitivity, thrombogenic potential

Kallikrein Inhibitor:

* Ecallantide - 30 mg subcutaneously
* Inhibits kallikrein to reduce bradykinin production
* Onset: 1-4 hours, duration ~24 hours
* Risk of anaphylaxis (2-4%)

Bradykinin B2 Antagonists:

* Icatibant - 30 mg subcutaneously
* Blocks bradykinin B2 receptor activity
* Onset: 0.5-2 hours, duration ~8 hours
* Local injection site reactions

Attenuated Androgens:

* Danazol, stanozolol, oxandrolone
* Increase C1-INH levels and reduce bradykinin production
* Reduce attack frequency/severity by 50-90%
* Monitor for androgenic adverse effects

Antifibrinolytics:

* Tranexamic acid - 1-1.5 grams IV or orally 2-3 times daily
* Inhibits conversion of plasminogen to plasmin
* Adjunctive therapy to reduce severity of acute attacks

**Hereditary Angioedema (HAE) Drug Chart**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Medication | C1-INH Concentrates (Berinert, Cinryze) | Conestat alfa (Ruconest) | Icatibant (Firazyr) | Ecallantide (Kalbitor) | Fresh Frozen Plasma (FFP) |
| Dose | 20 units/kg over 10 min | 50 units/kg over 5 min (max 4,200 units) | 30 mg (may repeat every 6 hours (max 90 mg/day) | 30 mg (may repeat one time within 24 hours) | 2 units |
| Administration | IV | IV | SubQ | SubQ | IV |
| Mechanism | CI-INH replacement | CI-INH replacement | Bradykinin B2 receptor antagonist | Plasma kallikrein inhibitor | CI-INH replacemen |
| Onset | 30-60 minutes | 90 minutes | 120 minutes | 30 minutes to 4 hrs | 2 to 4 hours |
| Comments | Must be warmed to room temp Preferred therapy for children and in pregnancy | Must be warmed to room temp Maximum of 4200 units in 24 hrs | Indicated in patients > 18 years of age Caution in ischemic heart disease | BBW: Anaphylaxis (must be administered by a medical professional) | Monitor for volume 2 nd line to other C1-INH therapies |
| Price Tag $ | ~ $3,500 per 500 units | ~ $7,100 per 2,100 units | ~ $2,000-4,000 per 10 mg | ~ $6,000 per 10 mg | ~ $ 55 per uni |

**ACE Inhibitor-Induced Angioedema:**

Discontinue Causative ACE Inhibitor:

* Angioedema resolves over 48-72 hours after stopping ACE inhibitor
* Do not rechallenge due to ~25% recurrence risk with re-exposure
* Switch to alternative antihypertensive (ARB, CCB, etc.)

Targeted Therapies:

Icatibant 30 mg subcutaneously:

* Small studies show faster symptom resolution compared to corticosteroids/antihistamines
* One randomized controlled trial found median time to complete symptom resolution reduced from 27 hours with standard therapy to 8 hours with icatibant
* Not FDA approved but supported by evidence

C1-INH Concentrates:

* Case reports of successful use in refractory ACE inhibitor-induced angioedema
* Small study found 20 units/kg IV berinert resolved ACE inhibitor-induced angioedema in 24 hours
* Not FDA approved for ACE inhibitor-induced angioedema

Ecallantide:

* Mixed data from trials; failed to show benefit over placebo in two randomized controlled trials
* Potential to try for refractory attacks given case reports of success

Fresh Frozen Plasma:

* The usual dose of plasma is 2 units for adults
* Provides functional C1-INH
* Case reports of benefit but high-quality evidence lacking
* Theoretical risk of worsening angioedema
* Consider for severe attacks refractory to other measures

Adjunctive Therapy:

* Antihistamines, corticosteroids - for symptom relief despite lack of effect on bradykinin-mediated angioedema
* Airway management - early otolaryngology involvement recommended for significant pharyngeal/laryngeal angioedema

**KEY GUIDELINES AND EVIDENCE**

This section summarizes current clinical guidelines and landmark evidence that guide the management of hereditary angioedema (HAE) and angiotensin-converting enzyme (ACE) inhibitor-induced angioedema.

**Guidelines for Hereditary Angioedema**

Several professional organizations have published evidence-based guidelines on the diagnosis and management of HAE, including:

* American Academy of Allergy, Asthma, and Immunology (AAAAI), American College of Allergy, Asthma, and Immunology (ACAAI), and Joint Council of Allergy, Asthma, and Immunology (JCAAI): Practice parameter – A focused parameter update: Hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor–associated angioedema.
* Key Recommendations
  + Summary Statement 15: Epinephrine, corticosteroids, and antihistamines are not efficacious and not recommended for the treatment of HAE. (C)
  + Summary Statement 16: Fresh frozen plasma is often effective in abrogating HAE attacks; however, fresh frozen plasma might acutely exacerbate some attacks, and for this reason, caution is required. (D)
  + Summary Statement 18: Neither anabolic androgens nor antifibrinolytic drugs provide reliably effective treatment for acute attacks of angioedema. (D)
  + Summary Statement 19: All patients with HAE should have access to an effective, on-demand HAE-specific agent. Evidence from double-blind, placebo-controlled randomized clinical trials demonstrates the efficacy and safety of treatment of HAE attacks with C1INH concentrates, a plasma kallikrein inhibitor, or a bradykinin B2 receptor antagonist (A).

**CLINICAL SCENARIOS**

Scenario 1: Acute Hereditary Angioedema Attack

A 32-year-old male with a history of HAE presents to the emergency department with severe abdominal pain, nausea, vomiting, and tongue swelling. He reports having difficulty speaking. On exam, he has a moderately enlarged tongue without stridor. He states his last HAE attack was 2 months ago, and he does not have any medication available to treat acute attacks.

Which acute medication would be the most appropriate to administer in this situation?

Answer and Explanation

* Icatibant 30 mg subcutaneously would be the preferred treatment, as it specifically inhibits bradykinin activity and can provide rapid symptom relief in patients with HAE attacks who lack access to C1-INH replacement therapy. Antihistamines, corticosteroids, and epinephrine do not affect bradykinin-mediated angioedema in HAE and should be avoided. While not ideal, icatibant can serve as an alternative option when the C1-INH products are not available.

|  |  |  |  |
| --- | --- | --- | --- |
| Author, year | Design/ sample  size | Intervention & Comparison | Outcome |
| Baş,   2015 | RCT   (n = 27) | SubQ Icatibant 30 mg vs. prednisolone +  clemastine      ACE-Inhibitor Induced Angiodema | Time to complete symptom resolution:  8 hours vs. 27.1 hours (P=0.002).   Time to onset of symptom relief:  2 hours vs. 11.7 hours (P=0.03).   All patients experienced complete  resolution of edema. |
| Hassen,   2013 | Case series  (n = 7) | 2 units FFP following antihistamine and  corticosteroid administration      ACE-Inhibitor Induced Angiodema | Temporal association between the administration of FFP and improvement in  angioedema in 7 cases of presumed   ACEI-induced angioedema that were  refractory to histamine-related  anaphlaxis. |
| Beauchêne,  2018 | Case Series  (n = 33) | Tranexamic Acid  IV: 24 patients (73%)  PO: 8 patients (24%)  Unknown: 1 patient (3%)   Dosage: 500 mg – 4 grams (55% received 1 g)      ACE-Inhibitor Induced Angiodema | 81.8% patients achieved significant  improvement following TXA administration  alone.   39.3% patients experienced symptom  improvement within 1 hr of TXA administration. |
| Le et al, 2017 | RCT (n=43) | IV recombinant human C1-INH (rhC1-INH) 50 units/kg (max of 4,200 units) or placebo to patients with a severe HAE attack | RhC1-INH significantly reduced the time to onset symptom relief (90 min vs 334 min) and also required less rescue therapy in HAE |
| Farkas et al 2017 | Observational  (n=32) | Pediatric patients (< 18 years old) received subcutaneous icatibant (0.4 mg/kg, max 30 mg) in HAE | Icatibant was well tolerated, injection-site reactions with erythema and swelling were most common (90.6% of patients) |
| Levy et al, 2010 | RCT  (n=96) | Subcutaneous ecallantide 30 mg or placebo in HAE | Ecallantide significantly mean symptom complex severity score at 4 hours and treatment outcome score throughout 24 hours in HAE |

**Tips for Board Exam Questions**

* Differentiate anaphylaxis and angioedema based on clinical features and underlying pathophysiology. Anaphylaxis involves multiple organs, hypotension, bronchospasm, etc. while angioedema manifests as localized swelling without hypotension.
* Remember epinephrine is first-line for anaphylaxis and antihistamines do not replace epinephrine. C1-INH, icatibant, ecallantide are used for hereditary angioedema, not anaphylaxis.
* For ACE inhibitor-induced angioedema, stopping the ACE inhibitor is key. Data for pharmacotherapies are limited in this condition.

**Summary**

Anaphylaxis is a systemic, potentially life-threatening allergic reaction requiring prompt epinephrine. Differentiate it from localized angioedema. Hereditary and ACE inhibitor-induced angioedema involve bradykinin and do not respond to epinephrine; specific treatments target this pathway. Management hinges on identifying the specific trigger and choosing appropriate pharmacotherapy based on pathophysiology.

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