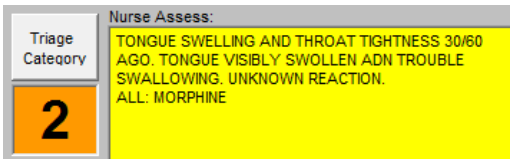
# Clinical update no. 523
# 10 October 2018




Angioedema; had started ramipril 3 weeks prior. Although a short time course in this patient, angioedema from ACE inhibitors can come on years after starting the drug. There was swelling of the tongue. Adrenaline was given IMI and by nebuliser, as well as hydrocortisone, with no improvement.

There were concerns for the airway and she was intubated uneventfully.

2 units FFP were given. In ICU she was given a dose of icatabant with good effect; there was reduction in swelling and she was able to be extubated a short time later.

A further episode 3 months later also responded to icatibant. What is its role?

In short, some people respond, as with this patient. Overall, trial results are mixed.

**Icatibant**

**Indications**

Acute attacks of hereditary angioedema

**Comments**

- inhibits bradykinin release which relieves symptoms of attack


EBMEDICINE.NET
AN EVIDENCE-BASED APPROACH TO EMERGENCY MEDICINE
Angioedema In The Emergency Department: An Evidence-Based Review
November 2012
Volume 14, Number 11
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https://umem.org/files/intl/Angioedema%20-%20Final%20copy.pdf

**Angioedema:** transient, localised, nonpitting swelling of the subcutaneous layer of the skin, or submucosal layer of the respiratory or gastrointestinal tracts.

There are 6 categories of angioedema: hereditary, acquired, immunologic/allergic, ACE-I induced, physically induced, idiopathic.

## Mediators Of Angioedema

Bradykinin is the primary mediator of most nonallergic forms of angioedema. C1 esterase inhibitor is involved, having a role in the complement pathway, and also histamine in some cases.

## Causes Of Angioedema

### Hereditary Angioedema

Most often due to C1 esterase inhibitor deficiency, often inherited as A/D, and leading to increased bradykinin

### Acquired Angioedema

Also due to C1 esterase inhibitor deficiency but not genetic and due to another mechanism. Autoimmune disease or malignancy, including haematological, are a cause of some acquired forms.

### Immunologic/Allergic Angioedema

A type 1 hypersensitivity reaction with anaphylaxis and often urticaria.

Some features that distinguish anaphylaxis and C1 esterase deficiency include anaphylaxis having a more acute onset with urticaria, bronchospasm and hypotension, and less likely to have laryngeal oedema. C1 esterase deficiency is slower onset, and more likely laryngeal oedema and abdominal pain, with treatment for anaphylaxis ineffective.

| | Angioedema in anaphylaxis | Angioedema due to C1INH deficiency |
|---|---|---|
| Urticaria | Frequent | Absent |
| Development of symptoms | Fast (within minutes) | Slow (within hours) |
| Duration of angioedema | 12-24 hrs | 48-72 hrs |
| Laryngeal edema | Rare | Frequent |
| Bronchospasm | Frequent | Absent |
| Abdominal pain | Rare | Frequent |
| Hypotension | Frequent | Absent |
| Treatment | Epinephrine, antihistamines, steroids | C1INH, icatibant |

### ACE Inhibitor-Induced Angioedema

Non-allergenic, mediated by bradykinin, which can also cause cough. Onset can be delayed several years from starting treatment with ACE-I. ARBs may also cause angioedema and the safety of ARBs in a patient who has had ACE-I induced angioedema is not established.

### Physically Induced Angioedema

Temperature extremes and physical activity can be a cause, possibly by histamine release.

### Idiopathic Angioedema

When no cause is identified.

## Differential Diagnosis

There are other causes of swelling. Of note, angiodemea may be localised. It can present as abdominal pain with ascites, diarrhoea and features of bowel obstruction.

## Emergency Department Evaluation

Assesing for airway compromise will guide the need for airway protection and intubation.

Otolaryngol Head Neck Surg. 2015 Oct; **Predictors of Airway Intervention in Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema.**

Involvement of the tongue, soft palate, vallecula, aryepiglottic folds, and true vocal cords (on flexible laryngoscopy) were associated with highest risk of needing airway intervention. Dysphagia, dysphonia, drooling, respiratory distress, and globus sensation also increased risk, as was early presentation (<4hr). Patients with oedema of the face, lower lip, and upper lip were at low risk.

Laryngeal oedema is unlikely if the patient can phonate a high pitched "E" sound.

An older study assesed risk as follows according to site of oedema:

| Site | Intervention (%) |
|---|---|
| Face, lip | 0 |
| Soft palate | 0 |
| Tongue | 7 |
| Larynx | 24 |

## Diagnostic Studies

Diagosis is often delayed years for hereditary angioedema. Low serum C4 level can prompt testing for C1-esterase inhibitor deficiency. There is no test for ACE-I angioedema.

## Treatment

Asses and protect the airway.

Treat allergy and anaphylaxis if thought to be the cause with adrenaline, fluids, steroids.

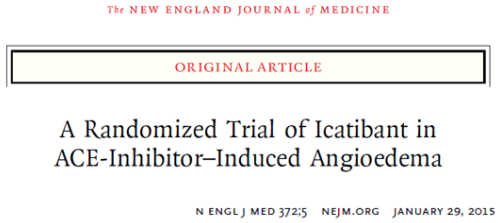
Antihistamines, steroids, and adrenaline have no role in bradykinin mediated angioedema.

### Fresh Frozen Plasma

Case reports support using FFP in acute attacks of hereditary and ACE inhibitor-induced angioedema. FFP contains C1 inhibitor, and also kininases that can break down bradykinin. Other substrates can theoretically worsen angioedema but this has not been observed in practice. The usual dose is 2 units FFP (10 to 15 mL/kg).

### C1 Inhibitor Concentrate

**Icatibant:** Trial data is mixed.


The NEW ENGLAND JOURNAL of MEDICINE

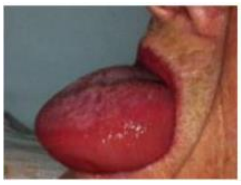
ORIGINAL ARTICLE

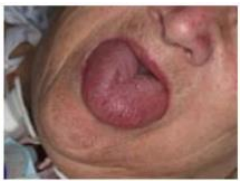
A Randomized Trial of Icatibant in ACE-Inhibitor–Induced Angioedema

N ENGL J MED 372;5 NEJM.ORG JANUARY 29, 2015

The outcome measure was time to resolution of symptoms which was 8hr with icatibant v 27 hr in control in patients treated within 6hr of onset of symptoms. 1/14 controls required tracheotomy v 0/13 with icatibant.

Case: resolve over12hr with conservative care





In another trial of 121 patients there was no benefit (J Allergy Clin Immunol Pract. 2017).

Time to resolution does not address whether icatibant might reduce the need for airway interventions. In our case immunology asked for it and it seemed to help on 2 occaisions.