Angioedema

Angioedema is a common indication for critical care admission. An allergist usually won’t be immediately available, so the critical care practitioner must be adroit in management of these cases.

Angioedema may be divided into histamine-mediated versus bradykinin-mediated etiologies. This is an essential differentiation, because the treatment for these two entities is entirely different. Histamine-mediated angioedema is essentially treated the same way as anaphylaxis (and it
may be a component of full-blown anaphylaxis). Alternatively, bradykinin-mediated angioedema requires specific therapies described further below.

diagnosis of angioedema

clinical features of angioedema

- Swelling of mucus membranes (e.g. eyelids, tongue, lips, pharynx, larynx, intestines).
- Varying anatomic distribution, depending on patient & etiology.
- Generally may be diagnosed based on swelling of observable anatomy (e.g. lips, tongue).

patient with upper airway obstruction (e.g stridor) & no observable swelling

- Differential diagnosis is broad here, for example (28291095 [https://www.ncbi.nlm.nih.gov/pubmed/28291095]):
  - Angioedema can cause localized swelling of the airway (e.g. larynx).
  - Infection (e.g. deep neck space infection)
  - Foreign body
  - Superior vena cava syndrome
  - Macroglossia (e.g. due to acromegaly, amyloid, or hypothyroidism)
  - Functional or factitious stridor
- Nasolaryngoscopy or bronchoscopy are preferred tests:
  - (a) Identify location of airway obstruction
  - (b) Define airway anatomy
  - (c) Allow planning of therapeutic strategy (e.g. whether or not patient’s airway is amenable to orotracheal intubation)
  - (d) In the case of bronchoscopy, this may be converted into bronchoscopic intubation if necessary.
- If the patient has already been intubated, then strongly consider a CT scan of the neck to exclude infectious foci which may require drainage.
- Fiberoptic airway examination may be difficult or impossible in the intubated patient.

histamine vs bradykinin-mediated angioedema

clinical characteristics of histamine-mediated versus bradykinin-mediated angioedema.

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Numbers obtained from Lenczowski 2018 PMID 29721614

Internet Book of Critical Care, by @PumCht
**approach to sorting out the etiology of angioedema**

- Clearly differentiating the cause of angioedema is important (because the treatments are entirely different).
- Histamine-mediated angioedema will almost always respond rapidly to aggressive treatment (with antihistamine, steroid, and possibly epinephrine). In contrast, bradykinin-mediated angioedema won’t respond to these treatments (and tends to progress slowly, over a period of hours). Therefore, an immediate therapeutic trial of therapies for histamine-mediated angioedema can be used as a diagnostic/therapeutic approach to undifferentiated angioedema (29721614).


**airway management**

[back to contents/etawg](https://emcrit.org/wp-content/uploads/2019/07/hmalgo.svg)

**indications for intubation**

- Precise indications are unclear. High-quality evidence is impossible to obtain, for the following reasons:
  - (#1) Physicians cannot be blinded to clinical features when they decide whether to intubate a patient.
  - (#2) Intubation is generally used as an outcome variable, but this may simply be a measurement of the decision algorithms which physicians employ when deciding whether to intubate (#1).
  - (#3) Truly determining which patients absolutely require intubation would require a decision to never intubate patients and seeing which patients die – which is obviously impossible.
- Potential indications for intubation are as follows:
  - (1) Stridor, dyspnea
  - (2) Inability to handle secretions
  - (3) Progressive deterioration of edema (intubation may become more difficult over time if edema worsens)
  - (4) Nasolaryngoscopy shows significant laryngeal edema or impending closure of the posterior pharynx. When in doubt, nasolaryngoscopy may help reveal whether there is significant laryngeal edema. The true threat to the airway is the larynx and posterior tongue – not the lips and anterior tongue.

**intubation is fraught with hazard**

- Airway manipulation may worsen swelling.
- Laryngeal edema will often preclude the use of a laryngeal mask airway.
- In severe angioedema, orotracheal intubation may simply be impossible.

**scenario #1: the crashing angioedema patient (extremely rare)**

- Description
  - Patient is at immediate risk of losing their airway.
  - Patient is stridulous, sitting bolt upright, and struggling for breath.
  - Patient may be unable to lie down.
- Potential management: Ketamine-dissociated cricothyrotomy
  - Place the patient on 100% FiO2 using one of the following:
    - i) High-flow nasal cannula at 100% FiO2 and 60 liters flow
• ii) BiPAP mask
• iii) 100% Non-rebreather facemask set to flush rate (crank the flow rate well past the 15 liters/min mark)
• iv) 100% non-rebreather facemask set to 15 liters/minute plus a nasal cannula underneath it running at 15 liters/minute

• Provide a dissociative dose of IV ketamine (e.g. 1.5-2 mg/kg) slowly over ~120 seconds. This should fully dissociate the patient, without impairing the respiratory drive. Patients with a history of alcoholism may require more ketamine to fully dissociate.
• Perform a scalpel-finger-bougie cricothyrotomy. The patient should continue breathing throughout the entire procedure, so you should be able to take your time a bit with this. However, if asphyxiation occurs, the procedure should be achievable very rapidly.

**scenario #2: the non-crashing angioedema patient**

- **Description**
  - The patient requires intubation, but isn't actively crashing.
  - There is time to call for help and additional equipment.
- **Suggested management:** The *awake double setup*:
  - Obtain an experienced intubator and someone competent at scalpel-finger-bougie cricothyrotomy *(Note: it doesn't matter whether this person is a surgeon, what matters is skill in this specific procedure).*
  - Perform awake fiberoptic intubation. These patients often have tongue swelling, so the best approach is often nasotracheal intubation (for taller patients, consider obtaining an extra-long ETT for nasotracheal intubation).
  - During the intubation procedure, the second operator should be prepared to perform cricothyrotomy if the airway is lost.

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**histamine-mediated angioedema**

The treatment and investigation of histamine-mediated angioedema is essentially identical to that of *anaphylaxis*. This is explored in further detail in the chapter on anaphylaxis. A brief summary of management is as follows:

- (1) **Epinephrine**
  - Indicated if there is significant threat to the airway (e.g. stridor, dyspnea, marked swelling).
  - Dose is 0.3-0.5 mg IM or an infusion of ~8-15 mcg/min.
- (2) **Corticosteroid** (e.g. 125 mg IV methylprednisolone)
- (3) **H1-receptor antihistamine** (diphenhydramine 50 mg IV q4-6hr)
- (4) **H2-receptor antihistamine** (famotidine 20 mg IV q12 hours or ranitidine 150 mg IV q6hr)

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**bradykinin angioedema: pathophysiology**
Bradykinin angioedema involves a **vicious spiral** involving plasmin, XIIa, and kallekrine as shown above. These proteins enzymatically activate one another, leading to an explosion of inflammatory kallekrine activity. This leads to the generation of bradykinin, which causes edema.

This vicious spiral may be triggered by different causes (as explored further below). However, all forms of bradykinin angioedema seem to share this common spiral of activity. This leads to shared clinical features and similar treatments. The following video summarizes some critical points in a minute (more complete discussion [here](https://emcrit.org/pulmcrit/bradykinin-spiral/)).
Types of bradykinin-mediated angioedema are listed below. The treatment for all of these disorders is fairly similar, so if your diagnosis is slightly incorrect that will be fine. Sorting out the different types of bradykinin-mediated angioedema can be done later on after the dust has settled. The key distinction is histamine-mediated versus bradykinin-mediated.

**medication-induced**

- ACEI-inhibitors or angiotensin receptor blockers (ARBs)
  - Most often due to ACE-inhibitors, but may also be due to angiotensin-receptor inhibitors.
  - Can occur years after starting an ACE inhibitor.
  - Careful history may often elicit prior episodes of angioedema which may have been less severe.
- Aliskiren (direct renin inhibitor)
- Thrombolysis (e.g. tPA)
- Dipeptidyl peptidase-IV inhibitor (i.e., gliptins for diabetes)
- Sirolimus, tacrolimus, everolimus
- Estrogens (oral contraception or hormone replacement therapy can exacerbate Type-III angioedema; see below)

**hereditary angioedema**

- Hereditary angioedema due to C1-inhibitor deficiency (onset generally <20 years old)
  - Type 1: Low C1-esterase protein level.
  - Type 2: Normal C1-inhibitor level but the protein is dysfunctional.
- Hereditary angioedema with normal C1-inhibitor function (formerly Type 3)
  - With factor XII mutation (which increases conversion of prekallekreine into kallekreine)
  - With unknown mutation

**acquired angioedema**

- Generally very rare (less common than hereditary angioedema), usually presents over the age of 40 years old ([28405953](https://www.ncbi.nlm.nih.gov/pubmed/28405953)).
- Type I: Associated with lymphoproliferative disorders (including chronic lymphocytic leukemia, non-hodgkins lymphoma, Waldenstrom's macroglobulinemia, follicular, and splenic marginal zone lymphoma)
- Type II: Associated with autoantibody against C1-inhibitor (may occur in lupus).

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**bradykinin angioedema: evaluation**

(back to contents/stop)

**history**

- ? Prior episodes
  - Hereditary angioedema will typically begin during adolescence.
- ? Medication history
- ? Family history
  - Family history of angioedema suggests hereditary angioedema (but absence doesn't exclude it, because mutations can occur de novo).

**diagnosis**

Labs won't return fast enough to affect management, but should be considered to guide future management. Administration of some therapies (e.g. fresh frozen plasma, C1-inhibitor concentrate) may impair the accuracy of subsequent laboratory values.
Angioedema - EMCrit Project

Laboratory investigation of various forms of bradykinin-induced angioedema

<table>
<thead>
<tr>
<th></th>
<th>Hereditary Angioedema-I (low C1-INH)</th>
<th>Hereditary angioedema-II (defective C1-INH)</th>
<th>Hereditary angioedema with normal C1-INH (often C1-INH)</th>
<th>Acquired angioedema</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4 level</td>
<td>Low*</td>
<td>Low*</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>C1-Inhibitor antigen</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
<td>Low or normal</td>
</tr>
<tr>
<td>C1-Inhibitor function</td>
<td>Low</td>
<td>Low</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>C1q</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>Paraprotein</td>
<td>May be found</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

brace your angioedema: treatment

Green Zone

- Clinical definition
  - Minimal edema
  - No real threat to airway

Yellow Zone

- Clinical definition
  - Airway threatened, but no indication for intubation (e.g., moderate lip/tongue edema)

Red Zone

- Clinical definition
  - Intubation is indicated

- Management
  1. First focus is intubation
  2. After securing airway, treat medically (to facilitate extubation)

- Patients can be grouped into roughly three classes based on disease severity. Classification may change over time (e.g., initially patients in the yellow zone will receive treatments, improve, and move into the green zone).

Overall treatment strategy

- The figure above summarizes how to approach patients at different severity levels.
- Intubation should be pursued if indicated (see indications for airway management above).
- Medical therapy has two potential roles:
  1. For patients with moderate disease (yellow zone), medical therapy may hopefully avert the need for intubation.
  2. For patients with severe disease (red zone), medical therapy may accelerate resolution and thus hasten the ability to extubate the patient. Without medical therapy, bradykinin-induced angioedema may take days to resolve.

Allergy-type therapies

- Steroid, antihistamine, and epinephrine don’t work for bradykinin-mediated angioedema.
- These therapies should be used if there is residual confusion about whether the angioedema could be histamine-mediated (see approach to undifferentiated angioedema above).

Medical therapy for bradykinin-induced angioedema

- Moderate to severe bradykinin-induced angioedema
  - Immediate treatment: 1 gram tranexamic acid IV
  - ACEI-induced
    - Consider fresh frozen plasma (2 units)
    - May repeat x1 if inadequate response
  - Not ACEI-induced
    - Consider C1-inhibitor concentrate (especially if known C1-inhibitor deficiency)

- If persistent, may consider addition of C1-inhibitor

- Internet Book of Critical Care, by @PulmCrit

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**Physiology:** Tranexamic acid inhibits the conversion of plasminogen into plasmin, which is a critical step involved in amplification of kallikrein activation. Theoretically, this should be beneficial in any form of bradykinin-mediated angioedema.

**Evidence:** Tranexamic acid has been used for hereditary angioedema for decades ([27672078](https://www.ncbi.nlm.nih.gov/pubmed/27672078), [20101876](https://www.ncbi.nlm.nih.gov/pubmed/20101876)). More recently, IV tranexamic acid has been used as a front-line emergency therapy to reverse episodes of ACEi-induced angioedema (with a case series reporting avoidance of intubation in all 31 patients who weren’t already intubated prior to receiving tranexamic acid) ([29735174](https://www.ncbi.nlm.nih.gov/pubmed/29735174)).

**Logistics:** Tranexamic acid is universally available, inexpensive, and safe. It’s often possible to administer tranexamic acid in <30 minutes (which is faster than it would take to thaw fresh frozen plasma, for example).

**Dose:** 1 gram IV immediately as a slow IV push over 10 minutes. May consider repeating if necessary, q4 hours PRN ([21905496](https://www.ncbi.nlm.nih.gov/pubmed/21905496)).

**Summary:** Immediate administration of tranexamic acid is reasonable for patients with bradykinin-mediated angioedema. The efficacy of this intervention is controversial, but this is a safe and inexpensive therapy.

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**C1-inhibitor concentrate**

**Physiology:** C1-inhibitor inhibits XIIa and kallikrein, perhaps the two most important enzymes involved in bradykinin generation. Based on its ability to inhibit multiple enzymes which are centrally placed in the spiral of kallikreine activation, this drug would be predicted to be very useful in bradykinin-induced angioedema.
Evidence: C1-inhibitor is generally acknowledged as front-line therapy for congenital angioedema with deficient C1-inhibitor activity. Case studies also suggest that this may be useful in ACEi-induced angioedema and thrombolytic-induced angioedema (28291095, 27502825, 27886906).

Logistics: C1-inhibitor is extremely expensive (especially in the United States). It often won't be available in smaller hospitals.

Dose:
- Berinert: 20 units/kg (preferred, FDA approved for acute exacerbations)
- Ruconest: 50 units/kg (contraindicated if rabbit allergy)
- Cinryze: 1000 units (not preferred, FDA approved for long-term prophylaxis)

Summary: C1-inhibitor seems like an excellent agent for any type of bradykinin-mediated angioedema, but it is limited by cost and availability.

Fresh frozen plasma (FFP)

Physiology: Patients with ACEi-induced angioedema have deficient activity of angiotensin converting enzyme (ACE), whereas patients with hereditary angioedema have deficient C1-inhibitor activity. Fresh frozen plasma contains both of these enzymes, so it may help normalize anti-bradykinin mechanisms in these situations. Fresh frozen plasma also contains substrates of the kallikrein system (e.g. high molecular-weight kininogen) which theoretically could exacerbate angioedema, but this doesn't usually seem to be a problem.

Evidence: Case reports generally suggest that FFP may be beneficial in ACEi-induced angioedema, although one recent report described deterioration despite FFP administration (27401592). A retrospective cohort study found that patients treated with FFP were less likely to require intubation (26953061). Similarly, case reports describe the use of FFP to prevent or treat exacerbation of hereditary angioedema (31316698).

Logistics: Widely available, not very expensive.

Dose: 2 units initially. May use an additional two units subsequently PRN.

Summary:
- i) Reasonable agent for use in ACEi-induced angioedema.
- ii) May be considered in hereditary angioedema, if C1-inhibitor concentrate isn't available.

Icatibant & ecallantide don't seem very helpful

Evidence and opinion on these agents is mixed. Currently, these may not be preferred agents for the following reasons:

1) They are not widely available (often even harder to obtain than C1-esterase inhibitor concentrate).
2) They are extraordinarily expensive.
3) They are administered subcutaneously (may take longer to work; subcutaneous administration is better for outpatient management of exacerbations but less useful for emergent inpatient therapy).
4) Evidence is mixed and overall not very persuasive:
   - Icatibant was ineffective against ACEi-induced angioedema in newer studies (27913306).
   - Ecallantide hasn't been very impressive in randomized controlled trials (25601538, 25182544).

5) Ecallantide carries a 3% risk of anaphylaxis (31316698).
6) If you're going to choose an expensive drug for treatment of bradykinin-mediated angioedema, C1-esterase concentrate seems to be supported by a greater amount of evidence and experience.

Patient-specific factors to consider:

- How severe was the swelling encountered during the initial intubation?
- Has the patient received medical treatment for angioedema? (e.g. steroid/antihistamine for allergic angioedema, or C1-esterase concentrates for C1-esterase deficiency)

General approach:
- If there is externally visible swelling (e.g. of tongue/lips), wait until this has substantially improved prior to considering extubation. If there is no external swelling, wait ~24 hours.
- Under deep sedation, very gently insert a hyperangulated videolaryngoscope blade (e.g. glidescope blade or C-MAC D-blade). This should allow for direct visualization of the airway including epiglottis.
- The primary determinant of readiness to extubate is visual confirmation that airway edema has improved (30480175). Presence or absence of cuff leak may provide some adjunctive information.

**extubation procedure**

- Consider extubation over an airway exchange catheter:
  - Leave the airway exchange catheter in place temporarily to ensure that the airway is patent.
  - If stridor occurs, re-intubation can be performed immediately over the exchange catheter.
  - Staff and materials should be available to perform reintubation or cricothyotomy if necessary.

**algorithms**

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Airway management should be considered early, yet must also be carefully pre-planned.

Failure to carefully differentiate between histamine-mediated versus bradykinin-mediated angioedema. These are two fundamentally different diseases, which require distinct treatments.

Airway manipulation can increase swelling, especially in bradykinin-mediated angioedema. Avoid unnecessary airway traumatization (e.g. aggressive suctioning of the airway).

Going further

- Reconceptualizing bradykinin-mediated angioedema as a universal vicious spiral [link](https://emcrit.org/pulmcrit/bradykinin-spiral/) (PulmCrit)
- Angioedema evaluation and management [link](http://www.emdocs.net/emdocs-cases-angioedema-evaluation-and-management/) (Brit Long and Michael Gottlieb, emDocs)
- Icatibant doesn't improve outcomes in ACEI-induced angioedema [link](https://rebelem.com/icatibant-doesnt-improve-outcomes-in-ace-i-induced-angioedema/) (Anand Swaminathan, RebelEM)
- Angioedema [link](https://coreem.net/core/angioedema/) (Heidi Sher, CoreEM)
- Hereditary angioedema [link](http://www.tamingthesru.com/blog/annals-of-b-pod/b-pod-cases/hereditary-angioedema/) (Christopher Shaw, Taming the SRU)

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The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.