Read My Lips: A Case-Based Approach to Managing Acute Angioedema
Disclosure

All planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.
Objectives

• Review current causes and treatments for patients presenting with general angioedema.
• Evaluate treatment for patients who present with acute hereditary angioedema.
• Select treatment for patients who present with angiotensin-converting enzyme inhibitor angioedema.
Don’t Take My Breath Away: Recognizing and Treating the Acute Angioedema Patient

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Patient Case 1

45 yo AAM arrives in your ED with a complaint of tongue and lip swelling he noticed when brushing his teeth. Patient denies any medical conditions, allergies, previous angioedema events, or events in his family. Patient’s wife states he was at the beach all day & ate at a new Thai restaurant.

Which type of angioedema might he be presenting with?
Patient Case 1

A. Immunologic/Allergy
B. Hereditary
C. ACE-Inhibitor Induced
D. Physically Induced
Angioedema

- 80,000-120,000 ED visits annually
  - ~18% are hospitalized
- May coexist with urticarial
- Enhanced vascular permeability results in subcutaneous or submucosal tissue swelling
- Skin appears normal
  - Non-pitting
  - Non-pruritic
- Commonly affects lips, tongue & eyelids

## Classification of Angioedema

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunological/Allergic</td>
<td>• IgE mediated reaction</td>
</tr>
<tr>
<td>Hereditary</td>
<td>• Deficiency in quantity or functionality of C1-INH due to genetic defect</td>
</tr>
<tr>
<td>Acquired</td>
<td>• Deficiency in quantity or functionality of C1-INH not due to genetic defect</td>
</tr>
<tr>
<td>ACE-Inhibitor Induced</td>
<td>• Adverse reaction to a medication</td>
</tr>
<tr>
<td>Physically Induced</td>
<td>• Extremes of temperature, physical activity, UV radiation or vibration</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>• Unknown etiology with multiple attacks</td>
</tr>
</tbody>
</table>

Wilkerson GR. *EM Pract.* 2012 Nov;14(11).
STEP 1: STABILIZE
Stabilization

- Vitals
- Airway assessment
- $O_2$ status
- ECG monitoring
- Prepare for intubation
- Placement in area for frequent assessment
<table>
<thead>
<tr>
<th>Stage</th>
<th>Site</th>
<th>Episodes (%)</th>
<th>Outpatient Tx (%)</th>
<th>Floor Tx (%)</th>
<th>ICU Tx (%)</th>
<th>Intervention (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Face, lip</td>
<td>31</td>
<td>48</td>
<td>52</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>Soft palate</td>
<td>5</td>
<td>60</td>
<td>40</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>Tongue</td>
<td>32</td>
<td>26</td>
<td>7</td>
<td>67</td>
<td>7</td>
</tr>
<tr>
<td>IV</td>
<td>Larynx</td>
<td>31</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>24</td>
</tr>
</tbody>
</table>

Tools for Oxygenation

- Flexible fiber optic laryngoscopy
- Laryngeal mask
- Nasopharyngeal oxygenation

https://www.aliem.com/2014/03/trick-trade-nasopharyngeal-oxygenation
Monitoring and Intubation

• Monitoring
  – General respiratory management
  – To intubate or not to intubate?

• Intubation
  – Nasal vs. oral intubation
  – Fiberoptic
  – Cricothyrotomy

http://www.aschoolofairway.com/airway_devices/fiberoptics_rigid_or_flexible

STEP 1: STABILIZE

STEP 2: DIFFERENTIATE
Differential Diagnosis

- Classes of angioedema +/- urticaria
- Anaphylaxis
- Edema
- Dermatitis
- Cellulitis
- Muckle-Wells syndrome

- Venous obstructive diseases
- Gleich syndrome
- Ascher syndrome
- Melkersson-Rosenthal syndrome
- Filariasis
History & Physical

- Prior attacks
- Family history (hereditary)
- Medical history
- Current medications
- Allergies & triggers
- Symptoms
- Onset & progression

- Edema location
- Laboratory findings
  - C1-INH levels
  - C4 levels
STEP 1: STABILIZE
STEP 2: DIFFERENTIATE
STEP 3: TREATMENT
Patient Case 2

You provider would like to intubate the patient at this time due to wheezing and angioedema, but the patient is very concerned and would like to see if anything else can be done prior.

Which medication would you recommend as the first medication?
Patient Case 2

A. Epinephrine 0.3 mg IV
B. Prednisone 60 mg PO
C. Epinephrine 0.3 mg IM
D. Diphenhydramine 25 mg IV
Treatment Options

- Is there evidence of anaphylaxis?
- What type of angioedema are you dealing with?
- What other medications is the patient on?
- If I’m not sure – I go with empiric treatment!
Epinephrine

• First-line in patients with respiratory distress, severe laryngeal edema or anaphylaxis
• Dosing:
  – 0.3 mg (0.2-0.5 mg) IM q15-20 minutes
  – 0.01 mg/kg (max of 0.3 mg)
• IM better than SQ in studies
• Lateral thigh superior to deltoid
  – Only need 60 mmHg to absorb
• Use 1 mg/mL concentration
  **Note: labeling changed to only reflect mg/mL
  (no more 1:1,000 vs 1:10,000 – Yay!!!)

Epinephrine IV

- Reserved for patients in cardiac arrest or receiving multiple IM doses commonly
- Must dilute!!!!!
- Dosing:
  - 1-4 mcg/min
  - Consider starting lower – beta activity
Glucagon

- May consider in patients taking beta-blockers
  - May have decreased response to epinephrine
- Glucagon affects cAMP independently of beta-receptor
- Dosing:
  - 1-5 mg IV over 5 min
  - 20-30 mcg/kg IV (max of 1 mg) in pediatrics
  - Infusion: 5-15 mcg/min

Histamine Antagonists

Second-line in anaphylaxis situations

• H1 Antagonist
  – Guidelines suggest second generation
    • Limitations in formulation and availability
  – Diphenhydramine most commonly use as IV

• H2 Antagonists
  – 15% of histamine receptors in skin are H2

Kanani, et al. *Allergy, Asthma & Clinical Immunology.* 2011.7(suppl 1):59
Corticosteroids

• Inhibits T helper cells & inflammatory mediators
• Second line agent
  – Delayed effect
  – May prevent rebound or longer reaction
• No high-quality data to show efficacy in angioedema
Biphasic Reactions

• Potential for 2\textsuperscript{nd} episode up to 8hr after

• Only 5 of 496 anaphylaxis visits had
  – 2 within ED visit
  – 3 after discharge
  – No deaths

• Probably don’t need long observation

STEP 1: STABILIZE
STEP 2: DIFFERENTIATE
STEP 3: TREATMENT
STEP 4: PREVENT
Prevention

• Remove offending allergen (if identified)
• Send patient home with self-administered epinephrine!!!!
  – Epi-pen (0.3 mg IM)
  – Epi-pen JR (0.15 mg IM)
• Education on use
• If possible fill/dispense prior to leaving ED
Key Takeaways

• Key Takeaway #1
  – Differentiation of types of angioedema are key to selecting therapeutic options. If unknown, empiric therapies should be started after stabilization.

• Key Takeaway #2
  – Epinephrine IM is the first-line agent for all patients with respiratory distress, severe laryngeal edema or anaphylaxis

• Key Takeaway #3
  – All patients should receive a self-administration epinephrine device
Swelling That's Not Swell: Managing Acute Hereditary Angioedema

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TY is a 17-year-old female with no known PMH that presents with face and neck swelling and laryngeal edema. Patient denies any known food or medication allergies. Patient is unable to report any family history of angioedema and other family members are not available at this time.

Which of the following would be the most appropriate empiric treatment option based on symptoms?
Patient Case cont.

A. Icatibant
B. C1INH (Berinert®)
C. Epinephrine, methylprednisolone, and diphenhydramine
D. Ecallantide
History Lesson

1586

1876

1882

1888

1961

Hereditary Angioedema (HAE)

• Rare, autosomal-dominant disorder
• Manifests in childhood and associated with high morbidity but low mortality
• Three types of HAE:
  ➢ Type I – deficiency of C1 esterase inhibitors (80-85%)
  ➢ Type II- malfunction of C1 esterase inhibitors (20-25%)
  ➢ Type III- normal C1 esterase activity (rare)
HAE Diagnosis

• Clinical criteria is usually first sign
  – Recurrent non-pruritic edema
  – Family history
• Diagnosis of exclusion
• Laboratory studies:
  – ↓ C1 esterase inhibitor concentrations
  – Improper C1 esterase inhibitor activity
  – Abnormal genetic markers

Pathogenesis

- Factor XIIa
  → Prekallikrein
  → Kallikrein
  → HMW kininogen
  → Bradykinin
  → Bradykinin B₂ receptor
  → Vasodilatation ↑ permeability
  → Edema
TY’s mother has arrived to the ED. She states that there is history of HAE in the family. Patient has increased laryngeal edema and is unable to protect her airway.

Which of the following would be the most appropriate treatment option based on symptoms?
Patient Case Cont.

A. Ecallantide
B. C1INH (Berinert®)
C. Fresh frozen plasma
D. Intubation/supportive care measures
Acute Treatment of HAE

• Empiric treatment for unknown diagnosis:
  – Epinephrine, antihistamines and corticosteroids
  – Usually not efficacious but leads to HAE diagnosis

• Secure airway/supportive care
  – Intubation if laryngeal edema

• C1 inhibitor therapy, icatibant, or ecallantide
  – Based on swelling location and availability

HAE Treatment

• Goals of treatment:
  – Avoidance of swelling
  – Reduction of attack frequency and severity

• Available treatment targets:
  – Replacement of C1INH
  – Bradykinin B₂ receptor blocker
  – Plasma kallikrein inhibitor
  – Increase concentrations of C4 complement
  – Inhibition of plasminogen

C1INH therapy

Factor XIIa → C1-INH → Prekallikrein → C1-INH → Kallikrein → HMW kininogen → Bradykinin → Bradykinin B$_2$ receptor → Vasodilatation ↑ permeability → Edema
C1INH Concentrates
(Berinert®/ Cinryze®)

- C1INH Replacement
- Clinical trials have shown significantly faster symptom resolution during acute treatment
- Median onset is 30-60 mins
- Must be brought to room temperature and reconstituted prior to administration
- Preferred treatment in children < 12 yrs of age and pregnancy

Conestat alfa

- Recombinant human C1INH
- Trials have shown that administration was safe and more effective than placebo in reducing HAE symptoms
- Contraindicated in patients with allergy to rabbits or rabbit-derived products
- Must be brought to room temperature and reconstituted prior to administration

Fresh Frozen Plasma (FFP)

- C1INH replacement
- Considered 2\textsuperscript{nd} line to the other C1INH therapies
  - No head to head trial comparing C1INH therapies to FFP
- Monitor volume overload
- Long thaw time and potential for transfusion-associated adverse outcomes

Ecallantide

- Factor XIIa
  - Prekallikrein
    - Kallikrein
      - HMW Kininogen
        - Ecallantide
        - Bradykinin
          - Bradykinin B₂ receptor
          - Vasodilatation
            - ↑ permeability
              - Edema
Ecallantide

- **EDEMA3:**
  - Improvement in patient reported treatment scores (p=0.004)
  - No difference in time to significant improvement (p=0.14)

- **EDEMA4:**
  - Greater change in severity score from baseline (p=.01) and treatment score (p=0.003)

- **Black Box Warning:**
  - Risk of possible anaphylaxis and should be administered in a controlled setting

Icatibant

Factor XIIa -> Prekallikrein -> Kallikrein -> HMW kininogen

Bradykinin

Bradykinin B2 receptor

Icatibant

Vasodilatation ↑ permeability

Edema
Icatibant

- FAST-1: Placebo vs. icatibant
  - Median time to clinically significant relief: 2.5 hrs icatibant vs. 4.6 hours placebo, p=0.14
- FAST-2: Oral TXA vs. icatibant
  - Median time to clinically significant relief: 2 hrs icatibant vs. 12 hours TXA, p<0.001
- FAST-3: Placebo vs. icatibant
  - Decreased time to symptom relief in cutaneous, abdominal and laryngeal HAE, p<0.001
- Caution use in patients with ischemic heart disease
  - Blockage of B2 receptor ↓ coronary blood flow

Patient Case Part 3

TY has now been intubated, stabilized, and supportive care measures have been started. The physician would like to start a pharmacological agent for the treatment of HAE.

Which of the following would be the most appropriate treatment option?
Patient Case Cont.

A. Ecallantide
B. Icatibant
C. C1INH (Berinert®)
D. Anything I can find in the pharmacy!
Key Takeaways

• Key Takeaway #1
  – If HAE diagnosis unknown, empiric treatment should consist of epinephrine, corticosteroids, and antihistamines

• Key Takeaway #2
  – Patients with significant laryngeal/oropharynx edema and airway issues, focus should be intubation/supportive care vs. pharmacological treatment

• Key Takeaway #3
  – No head to head studies have compared inpatient HAE treatments, selection based on formulary and drug availability
ACE the Approach: Managing ACE-I-induced Angioedema

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CLINICAL CASE

• 59 year old AAF
• Inspiratory dyspnea, lingual edema, globus sensation with onset 1 hour prior to arrival
• Vital signs within normal range, maintaining 100% SpO₂ on 2L NC
• Home medications include lisinopril 20mg PO daily
ACE-I ANGIOEDEMA: WHAT WE KNOW

• Likely precipitated by the accumulation of bradykinin
• Conventional treatment largely ineffective
ACE-I ANGIOEDEMA: WHAT WE KNOW

- Data limited, but possible treatments include FFP, kallikrein inhibitors, C1-esterase inhibitor concentrate, and icatibant
ACE-I ANGIOEDEMA: WHAT WE KNOW

• Loss of airway is the most life-threatening problem, should be primary focus for acute management in the ED
FLIGHT PLAN

- Mechanism and defining characteristics
- Possible treatment options and available data
- Where we are today and possible approach to care
ACE-I ANGIOEDEMA MECHANISM

Vascular permeability

Vasodilation

Angioedema

1. Kininogen → Kallikrein → Bradykinin → Bradykinin Metabolites → Angioedema
2. Angiotensinogen → Angiotensin I → Angiotensin II

ACE inhibits the conversion of Angiotensin I to Angiotensin II, reducing vasodilation and vascular permeability.
HISTAMINE vs. BRADYKININ

HISTAMINE
- IgE mediated
- Pruritic urticaria common
- Responsive to “standard” treatment
- Idiopathic, drug-induced (NSAIDS, aspirin), allergic

BRADYKININ
- Not associated with IgE
- Increased bradykinin production or insufficient degradation
- No urticaria
- Not responsive to “standard” treatment
CHOOSE YOUR WEAPON

- FFP
- Ecallantide
- C1 Esterase Inhibitor Complex
- Icatibant
FRESH FROZEN PLASMA

- Provides kininase II

**Diagram**:
- Kininogen
  - Kallikrein
  - Bradykinin
  - Bradykinin Metabolites
- ACE
FRESH FROZEN PLASMA

• Limited evidence
  – 4 case reports, 10 patients\(^1\)
  – Average dose 1-4 units (10-15 ml/kg)
  – Initial improvement – median 2 hours
  – Lack of good controls
<table>
<thead>
<tr>
<th>PRO’s</th>
<th>CON’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inexpensive</td>
<td>Infectious transmission</td>
</tr>
<tr>
<td>Ubiquitous</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Logical</td>
<td>Volume overload</td>
</tr>
<tr>
<td>mechanism</td>
<td>Thawing time</td>
</tr>
<tr>
<td></td>
<td>Delayed onset of symptom reduction</td>
</tr>
<tr>
<td></td>
<td>Symptom exacerbation</td>
</tr>
</tbody>
</table>
• Kallikrein inhibitor
ECALLANTIDE

• Bernstein, et al²
  – Randomized, triple-blind, placebo-controlled
  – Ecallantide 30mg (n=26) vs placebo (n=24)
  – Primary end point – discharge within 4 hours
    • 8 (31%) ecallantide, 5 (21%) placebo – Not significant
  – Open label ecallantide if symptoms worsening
    • 11 (42%) ecallantide, 13 (54%) placebo
ECALLANTIDE

• Lewis et al.³ - multicenter, phase 2, double-blind trial
• Ecallantide 10mg (n=20), 30mg (n=19), 60mg (n=19), vs placebo (n=18)
• Primary endpoint – discharge within 6 hours
• Study terminated: High response rates in all arms
• High rate of adverse effects
  – New or worsening angioedema – n=20 ecallantide; n=4 placebo
C1 ESTERASE INHIBITOR CONCENTRATE

• Blocks conversion of kininogen to bradykinin
• 2 case reports, 2 case series\(^1\)
  – Total 23 patients
  – 22 patients - symptom improvement mean of 80 minutes
  – 1 patient – no symptom improvement, no further details
  – No adverse events reported
• Phase 3 recruiting, estimated completion late 2018
Bradykinin-2 receptor antagonist
Hereditary angioedema treatment

Cost
$9,440.78 (wholesale acquisition)
$4,689.88 (340b)
ICATIBANT

Kininogen

Kallikrein

Vascular permeability

Bradykinin

ACE

Vasodilation

Angioedema

Bradykinin Metabolites
ICATIBANT EVIDENCE

• Case reports
• 3 case series
• 1 published, phase-II, randomized controlled trial
• 1 published, phase-III, randomized controlled trial
ICATIBANT – CASE REPORTS

• 26 patients\(^1\)
  – 25 with symptom improvement, range 10-30 minutes
  – 1 without improvement
ICATIBANT – CASE SERIES

Bas et al\textsuperscript{4}

- 47 patients (historical comparator)
  - Standard treatment
  - Full resolution – 33 hours
  - Airway intervention – 5 patients

- 8 patients, icatibant 30mg subcutaneously
  - Initial symptom relief – 50.6 +/- 21 minutes
  - Full resolution – 4.4 hours
  - Airway intervention – zero patients
### ICATIBANT – CASE SERIES

DeBard et al.\(^5\)

<table>
<thead>
<tr>
<th>Pre-protocol</th>
<th>Post-protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>44 patients</td>
<td>7 patients (icatibant)</td>
</tr>
<tr>
<td>18 admitted</td>
<td>Zero airway intervention</td>
</tr>
<tr>
<td>6 (13.6%) airway intervention</td>
<td>LOS – 0.5 days</td>
</tr>
<tr>
<td>LOS – 7.7 days</td>
<td>Cost - $5,951</td>
</tr>
<tr>
<td>Cost - $17,878</td>
<td></td>
</tr>
</tbody>
</table>
ICATIBANT – CASE SERIES
Bova et al.\textsuperscript{6}

Icatibant 30mg SQ following standard treatment
• 13 patients
• Symptom onset to icatibant – 3 hours
• Icatibant to onset of relief – 30 minutes
• Full resolution – 5 hours

Standard treatment (historical)
• 10 patients, 27 episodes
• Symptom onset to initial relief – 11 hours
• Full resolution – 54 hours
ICATIBANT – PHASE 2 RCT

Bas et al.⁷

• Multicenter, double-blind, double-dummy
• Icatibant 30mg vs. “standard therapy”
• Primary end point
  – Time to complete resolution of symptoms
ICATIBANT – PHASE 2 RCT

Icatibant 30mg SQ

- 13 patients
- Primary end point – 8 hours*
- Complete resolution within 4 hours – 5 (38%)†
- Onset of relief – 2 hours§

Prednisolone 500mg + Clemastine 2mg

- 14 patients
- Primary end point – 27.1 hours
- Complete resolution within 4 hours – zero
- Onset of relief – 11.7 hours

*P = 0.002  † P = 0.02  § P = 0.03
ICATIBANT PHASE 3 RCT

Sinert et al. 8

- 31 centers, 4 countries
- Randomized 1:1 to icatibant 30mg or placebo, both administered subcutaneously
ICATIBANT PHASE 3 RCT

• Primary endpoint
  – Time to meet discharge criteria
• Secondary endpoint
  – Time to onset of symptom relief
  – Occurrence of airway intervention
ICATIBANT PHASE 3 RCT

Icatibant 30mg SQ

- 60 patients
- Primary end point – 4 hours†
- Onset of relief – 2 hours‡

Placebo

- 58 patients
- Primary end point – 4 hours†
- Onset of relief – 1.6 hours‡

† P = 0.63 ‡ P = 0.57
ICATIBANT PHASE 3 RCT

• Median time from attack onset to study drug
  – Placebo: 7.9h [range, 2.0 – 12.4]
  – Icatibant: 7.8h [range, 1.7 – 12.2]

• 1 patient (icatibant group) received airway intervention
  – 4.75 hours after attack onset
  – 1.5 hours after icatibant administration
ICATIBANT PHASE 3 RCT

• Author’s conclusion:
  – Icatibant had no appreciable benefit in treating ACE-I-induced angioedema
NOW WHAT?
Limited evidence vs. Intubation avoidance
PREDICTING AIRWAY RISK – CASE SERIES

- Kieu, et. al.\textsuperscript{9}
- Assess predictors for airway intervention
  - Time of presentation
  - High-risk clinical signs and symptoms
  - Anatomical regions in the head and neck that may indicate need for intubation
PREDICTING AIRWAY RISK – CASE SERIES

- 311 adult patients diagnosed with ACE-induced angioedema
- 52 patients (16.7%) required airway intervention
- Presenting within 4 hours of symptom onset correlated with 2-fold increase in likelihood of requiring intubation
PREDICTING AIRWAY RISK – CASE SERIES

• Highest risk symptoms
  – Dysphagia
  – Dysphonia
  – Globus sensation
  – Drooling
  – Respiratory distress
PREDICTING AIRWAY RISK – CASE SERIES

• Highest risk anatomical locations
  – Tongue
  – Soft palate
  – Vallecula
  – Aryepiglottic folds
  – True vocal cords

• Lowest risk locations
  – Face
  – Lower lip
  – Upper lip
WHERE DOES THIS LEAVE US?
RETURN TO THE CASE

- Lisinopril discontinued
- Icatibant 30mg SQ administered
- Subjective report of symptom reduction within 45 minutes
- Admitted, monitored in ICU, discharged following day
WHAT WOULD YOU DO?
ACE-inhibitor-induced angioedema is mediated by bradykinin accumulation and is largely unresponsive to "conventional" therapy.
Key Takeaway #2

There is a paucity of data regarding the use of FFP, ecallantide, C1 esterase inhibitor concentrate, and icatibant in ACE-I-induced angioedema.
Consideration *may* be given for use of icatibant in patients who are at high risk of requiring airway intervention, e.g., patients presenting within 4 hours of symptom onset, who present with drooling, respiratory distress, dysphagia, dysphonia, or globus sensation, or who present with affected tongue, soft palate, vallecula, aryepiglottic folds, or true vocal cords.
REFERENCES

THOUGHTS?
QUESTIONS?