Allergic Reactions

Edward C. Adlesic, DMD
Oral and Maxillofacial Surgery
University of Pittsburgh School of Dental Medicine

Case Presentation

- 50 y.o. female for excision of odontogenic cyst
  - PMH: HTN, GERD, & asthma
  - Denies past surgery or hospital stays
    - Medications: Metoprolol, Zantac, Advair, and Albuterol
    - Allergies: denies
    - ASA 2 patient
    - Physical examination unremarkable & VSS
- Propofol induction & sevoflurane maintenance
  - intubated without difficulty → penicillin given intraoperatively
  - surgery & anesthesia without complications → transfer to PACU
  - surgery took approximately 1 hour

Case Presentation

- PACU 30 minutes later → swelling in tongue
  - swelling not secondary from surgery → surgeon inspected site & no bleeding, erythema, or swelling around surgical area
  - tongue is swollen but it does not extend to the surgical site
  - swelling continues to enlarge
- How do you manage it???
  - Quick differential diagnosis for this event
  - What interventions are a priority?

Diagnosis & Treatment

- What is the diagnosis?
  - angioedema of the tongue
- Is this an allergic reaction?
  - penicillin intraoperatively
  - was given 1.5 hours ago
- Is the airway compromised?
  - patient is on 100% O_2 by full face mask → SpO_2 is 95%
  - patient is sedate but responsive to commands
- Tongue swelling is still getting worse
  - patient is getting anxious & is starting to have some dyspnea
- What would you do?

Angioedema of the tongue. Tongue protruding out of the mouth.

Direct laryngoscopy? Can you see the cords? How do you secure the airway?

Management

- Airway management
  - swelling is increasing
  - need to secure the airway
  - LMA or intubation??
- IGEL – LMA
  - will secure the airway for now
  - will not secure the airway if laryngeal edema occurs
    - can not visualize the cords
  - will increase laryngeal edema in some types of angioedema
- ET tube
  - will secure the airway
  - want to visualize the cords or use video laryngoscopy
  - avoid blind nasal
    - can increase angioedema

Management

- Medications are indicated as well
  - allergic reaction is possible cause
    - epinephrine 0.3 to 0.5 mg IM
      - epinephrine is priority
      - other agents are secondary
    - dexamethasone 8 mg IV or any appropriate steroid
    - diphenhydramine 50 mg IV
- No relief after 5 minutes
- Epinephrine is repeated 2 more times 0.5 mg IM
  - swelling is still progressing
  - there is no relief
- What is going on here?????????

Initial swelling in the PACU

Swelling after intubation in PACU

Case Presentation

- Patient did not respond to epinephrine, steroid, antihistamine
- Patient is intubated & airway is stable & secured
- Is this an allergic reaction?
- What is your diagnosis?
  - Were one of her maintenance medications the cause?
  - Is there another process going on here?

Allergic Reactions

Allergic Reactions

- Abnormal or hypersensitive reactions of the immune system to an "allergen or antigen"
- 15 to 25% of the US population are affected
  - 4.5% from allergic asthma
  - 4% from insect bites
  - 5% from medications
- Penicillin use has 5 to 10% risk of allergy
  - 0.04 to 0.2% risk of anaphylaxis
- Latex allergy affects 1 to 6% of the population

Gell & Coombs Classification of Immunologic Reactions

- Type I reactions
  - immediate onset reactions
    - majority occur within 1 hour of drug use (5 to 30 minutes)
    - some reactions occur > 1 hour
      - usually PO meds or slow absorption
- IgE antibody mediated
- mast cell & basophil release of vasoactive mediators
  - histamine, prostaglandins, & leukotrienes
- clinical signs
  - urticaria, pruritus, angioedema, or anaphylaxis
- antigens
  - food, insect stings, venom, medications, occupational allergens

Type II Reactions

- uncommon reaction
- Cytotoxic Reaction
- IgG or sometimes IgM antibody mediated cell destruction
- Ag binds to cell membrane → antibody attacks the cell & destroys it
- delayed onset: several days -- sometimes weeks
- clinically
  - hemolytic anemia, thrombocytopenia, or neutropenia

Type III reactions

- uncommon reaction
- Immune Complex reaction
- IgG antibody – antigen immune complex reaction
- complement system is activated
- Ag-Ab complex
  - is deposited in vessels and tissue to induce inflammation
- delayed reaction that takes weeks or months to present
- clinically
  - serum sickness, vasculitis, or Arthus reactions

Type IV Reactions

- common reactions
- unlike Types I, II, and III
  - not mediated by antibodies
- reaction is from activation and expansion of T lymphocytes
- delayed hypersensitivity reaction
  - may see reaction in 8 to 12 hours
  - 48 to 72 hours usually
  - may take longer
- clinically: contact dermatitis
  - erythema and edema with vesicles that rupture and crust
  - maculopapular eruptions

Drug Reactions Based On Time of Onset

- World Allergy Organization (WAO) definitions
  - immediate reaction is within 1 hour of drug administration
  - delayed reactions occur after 1 hour but usually more than 6 hours and occasionally weeks

Immediate Drug Reactions

- reactions occur < 1 hour after drug exposure
  - manifest as urticaria, angioedema, or anaphylaxis
  - onset may be within a few minutes or take 1 hour
    - time dependent upon route of administration
    - faster the onset → greater the reaction
    - greater the risk of a life threatening reaction
- additional clinical findings
  - rhinitis and conjunctivitis
  - pruritus
  - possible bronchospasm, hypotension, tachycardia
- type I IgE hypersensitivity reactions

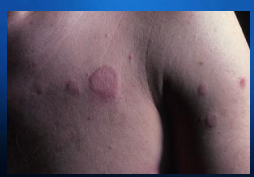
Non Immediate Reactions

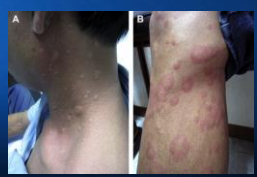
- onset > 1 hour after exposure
  - usually at least 6 hours but may take days after drug given
- clinical findings
  - urticaria may still be seen from an IgE reaction
    - rare to see IgE anaphylaxis in these cases
  - more common reactions are non IgE
    - maculopapular eruptions
    - Stevens-Johnson reaction
- Type II, III, or IV reactions → unlikely to be an IgE reaction
- most are T cell mediated reactions
  - delayed hypersensitivity

Immediate Allergic Reactions

Uticaria (Hives)

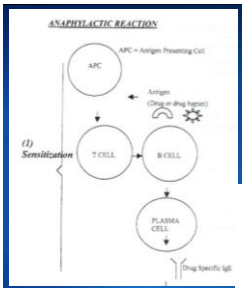
- transient blanch able, raised, smooth pink to red papules on skin
- "classical presentation of wheal"
  - pale raised lesion of skin surrounded by erythematous flare
- pruritus is common finding
- resolve within 24 hours after allergen removed





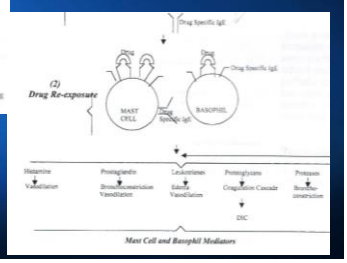
Histamine & Urticaria

- Type I IgE immune response to allergen (Ag)
- Ag exposure "sensitizes" the patient
  - T cells are activated to produce IgE
  - B cells differentiate into plasma cells
    - produce specific IgE antibodies (Ab)
  - IgE – Ab can bind to receptor sites on mast cells & basophils
- Ag exposure now will cause an Ag – Ab reaction
  - get release of mediators from mast cells and basophils
- clinically
  - edema of upper & mid dermal layers of skin
  - no mucosal lesions



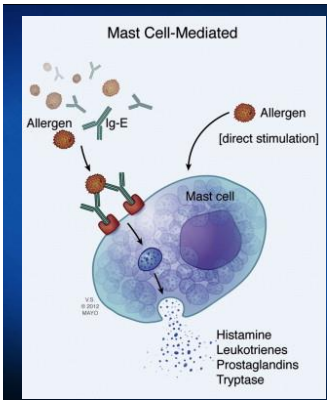
(1) Sensitization results in formation of drug specific IgE. Patient is now sensitized if antigen (drug) is reintroduced. Drug specific IgE can bind to receptors on mast cells & basophils.

(2) Drug now cross links 2 of the drug specific IgEs and get release of mediators



Step 1: form a drug specific IgE antibody

Anesth Analg. 2003;97:1381



Can measure some of the mediators to define the type of reaction

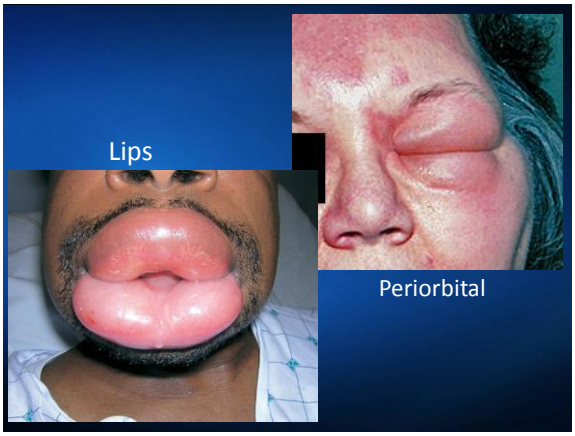
J Clin Anesth. 2013;25:335-343

Management: Antihistamines

- H_1 antihistamines → diphenhydramine
  - treat pruritus & hives
  - no effect on UAO, hypotension, or cardiovascular collapse
  - do not inhibit mast cell mediator release
  - adult dose: 25 to 50 mg IV (max dose = 400 mg/day)
  - child dose: 1 mg/kg IV if < 40 kg (max dose = 200 mg/day)
- H_2 antihistamine → ranitidine
  - additional relief of pruritus & hives
  - adult dose: 50 mg IV (may cause hypotension)
  - child dose: 1 mg/kg IV over 5 minutes (12.5 to 50 mg)
    - dilute in 20 mls & give slowly
- may need PO doses Q 6 h for a few days

Angioedema

- transient swelling of deep dermis, subcutaneous, or submucosal tissues
- non pitting edema
  - head, neck, lips, tongue, mouth, pharynx, or larynx
  - isolated area or spread to all of these sites
- 2 mediators for angioedema
  - IgE reaction → histamine allergic reaction
    - swelling occurs in minutes
    - resolves < 24 hours
  - bradykinin reaction → non allergic
    - occurs typically in hours
    - last for > 24 hours
- non pruritic most cases



Urticaria vs Angioedema

- urticaria is not life threatening
  - angioedema involving the airway is life threatening
- urticarial + angioedema at same time
  - more severe reaction
  - ↑ duration of swelling
  - ↓ response to treatment
    - may need to add steroids and epinephrine especially for laryngeal edema (will not respond in all cases → HAE)
- 50% urticaria + angioedema
- 40% isolated urticaria
- 10% isolated angioedema

Management of Angioedema

- If there is angioedema of the floor of mouth, tongue, pharynx, or larynx
  - airway will need to be secured
  - LMA not a good choice long term
    - intubating LMA is fine
  - need ET tube
- Suspect an allergic reaction → very reasonable suspicion
  - epinephrine is drug of choice
  - antihistamines & steroids are secondary
- Look for a cause
- Some cases epinephrine will not be the answer
  - What Are We Dealing With Now??
  - How Do You Proceed??

Anaphylaxis

- severe allergic – hypersensitivity reaction
- rapid onset & potentially fatal
- cutaneous lesions occur 80 to 90% cases
  - urticaria, angioedema, & pruritus
- respiratory & cardiovascular reactions
  - wheeze, dyspnea, hypotension, and tachycardia
- anaphylaxis is a clinical diagnosis
  - recognition of signs is critical to survival
  - early treatment with appropriate medications is mandatory

Triggers of Anaphylaxis

- children & young adults → food is the most common
  - peanuts
  - milk
  - eggs
  - reactions may recur after initial resolution (biphasic reaction)
- middle aged & older
  - medications
  - insect bites & venom
  - contrast dyes
  - occupational allergens

2 Types of Anaphylaxis

- Anaphylaxis
  - Type I IgE reaction
  - mediator release from mast cells
    - basophils may also be involved
- Anaphylactoid or Non immune anaphylaxis
  - non immune direct release of mediators from mast cells & basophils
  - activation of classical complement pathway
  - bradykinin mediated vasodilation & edema
  - treated just like allergic anaphylaxis

Subtypes of Anaphylaxis

- Biphasic anaphylaxis
  - recurrence after initial resolution
    - 4.5 to 23% of anaphylactic reactions
  - 11% occurrence in children
  - will occur within 8 to 10 hours after 1st reaction
- Protracted anaphylaxis
  - lasts for hours or days (weeks)
  - rare reaction

Clinical Signs of Anaphylaxis

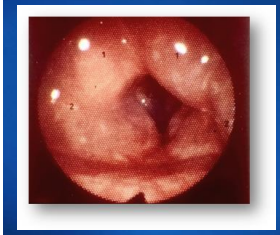
- Skin lesions: 80 to 90% cases
  - skin signs are absent or unrecognized in ~ 20% of cases
- Lower airway: 50% cases
  - dyspnea, wheeze, spasm, & hypoxia
- Upper airway: 20% cases
  - tongue & laryngeal edema
- GI & CVS: 30% cases
  - N/V, diarrhea, & abdominal pain
  - dizziness, syncope, hypotension, & tachycardia
- "Anaphylactic Shock"
  - fall in BP > 30% baseline

CVS Symptoms of Anaphylaxis

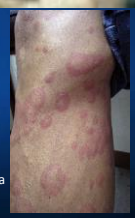
- less common than cutaneous signs
- CVS symptoms
  - hypotension & tachycardia
  - chest pain, LOC, tachydysrhythmias, & CVS collapse
  - cardiac arrest is rare (but it is the leading cause of fatal anaphylaxis)
- preexisting cardiovascular disease
  - number of cardiac mast cells is increased in CAD
    - decrease coronary blood flow
    - depress myocardial contractility
    - induce dysrhythmias
    - increase risk of arrest

Curr Opin Allergy Clin Immunol. 2014; 14: 309

Anaphylaxis



Laryngeal edema courtesy of Dr. Bosack



Other signs: angioedema & urticaria

Grading Anaphylaxis

Moderate to Severe Grade is a true anaphylactic reaction

J Allerg Clin Imm. 2004;114:371

TABLE V. Grading system for generalized hypersensitivity reactions

Grade	Defined by
1—Mild (skin and subcutaneous tissues only)*	Generalized erythema, urticaria, periorbital edema, or angioedema
2—Moderate (features suggesting respiratory, cardiovascular, or gastrointestinal involvement)	Dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain
3—Severe (hypoxia, hypotension, or neurologic compromise)	Cyanosis or $SpO_2 \leq 92\%$ at any stage, hypotension (SBP < 90 mm Hg in adults), confusion, collapse, LOC, or incontinence

Grade 4 = Cardiac Arrest

Table 1
Clinical diagnosis of anaphylaxis

Anaphylaxis is highly likely when there is an acute onset of clinical symptoms involving *at least* 2 organ systems together with skin and mucosal tissue involvement

Skin and mucosal tissue	Urticaria, angioedema, generalized pruritus or flushing, rhinitis, conjunctivitis
Respiratory system	Lower airway: dyspnea, wheezing, bronchospasm, reduced peak expiratory flow, hypoxemia Upper airway: stridor or upper airway obstruction from laryngeal edema or tongue swelling, together with hypersialorrhea, dysphonia, or dysphagia
Gastrointestinal symptoms	Crampy abdominal pain, nausea, vomiting, diarrhea
Cardiovascular system	Dizziness, syncope, hypotension (collapse)

Anaphylactic shock is defined as anaphylaxis accompanied by reduced blood pressure. On rare occasions, patients can present with isolated acute hypotensive episodes

Infants and children	Low systolic blood pressure (age specific) or >30% decrease in systolic blood pressure
Adults	Systolic blood pressure <90 mm Hg or >30% decrease from patient's baseline

Med Clin N Am. 2010; 94: 691-710

3 Criteria → Need 1 for Diagnosis

- #1: Acute onset urticaria ± angioedema of skin – mucosa
  - hives, pruritus, erythema
  - also need to see: respiratory compromise or cardiovascular signs
    - dyspnea, wheeze, bronchospasm, or hypoxia
    - decreased BP, tachycardia, or syncope
- #2: See 2 or more of these signs after exposed to likely Ag
  - skin – mucosal lesion: urticarial ± angioedema
  - respiratory compromise
  - reduced BP, tachycardia, or syncope
  - GI symptoms: abdominal pain or vomiting
- #3: Reduced BP after exposed to known Ag
  - systolic BP < 90 mm or greater than 30% decrease from baseline

UptoDate accessed Jan 2015

Perioperative Anaphylaxis

- 1:5000 to 1: 20,000 anesthetics
  - IgE anaphylaxis 60% cases
  - Anaphylactoid 10.6% cases
  - fatal in 3 to 10% of cases
  - occurs within minutes → even 1 minute after IV dose of drug
- awake patients → will see early signs of anaphylaxis
  - malaise, pruritus, dizziness, & dyspnea
  - unable to detect if under anesthesia
- initial signs during anesthesia
  - difficulty in ventilation & wheeze
  - desaturations
  - hypotension & tachycardia
  - ↓ end tidal CO_2
  - pulselessness

Anesth Analg. 2008;107:620

AANA J.2012;80:129

Perioperative Anaphylaxis

- Clinical Signs frequently seen
  - hypotension 97%
  - urticaria 17%
  - bronchospasm 43%
- Females > men
- Agents determine when it occurs
  - usually on induction
  - latex is usually later in the case (30 to 60 minutes)

Differences between perioperative/perianesthesia anaphylaxis and anaphylaxis in other settings

	Other settings	Perioperative
Skin	Flushing, itching, or urticaria are present in >90 percent of cases	• Signs and symptoms are more likely to be absent • Patient cannot report itching • May be present but hidden by surgical drapes
Upper respiratory tract	Laryngeal edema can present as throat tightness, deepening of voice	Severe laryngeal edema may present as difficulty with intubation
Lower respiratory tract	Shortness of breath, wheezing, persistent cough are typical	May present as sudden: - Increase in ventilatory pressure needed to inflate lungs - Increase in end-tidal CO_2 - Decrease in arterial oxygen saturation
Cardiovascular system	Dizziness or tunnel vision may signal onset of hypotension (collapse without warning symptoms is not typical)	• Cardiovascular collapse is the first detected manifestation in one-half of cases • Arrhythmias and cardiac arrest more common

UptoDate Accessed Jan 2015

Here: increase in end tidal CO2; other sources decrease in end tidal

Agents Causing Perioperative Anaphylaxis

Agent	1	2	3	4
NMBA	58%	70%	62%	23%
Anesthetic Agents	---------	----------	7.4%	--------
Antibiotics	15.1%	15%	4.7%	59%
Latex	16%	23.3%	16.5%	18%
Opioids	---------	----------	1.9%	--------

1. Anesthesiology. 2003;99:536
2. Hippokratia.2011;15:138
3. Anesth Int Therapy.2012;44:104
4. J Allergy Clin Immun Pract. 2015; Jan

Anesthetic Agents

- NMBA Anaphylaxis
  - usually on induction
  - women > men
  - IgE mediated response
  - cross sensitivity between agents
  - 15 to 50% of NMBA anaphylaxis
    - no previous history of exposure to drug (cosmetic products ?)
  - succinylcholine > rocuronium > atracurium > vecuronium > cisatracurium
    - Succinylcholine accounts for up to 60% of cases
  - sugammadex is a reversal agent for non depolarizing NMBA
    - "controversial" evidence but it may decrease the anaphylactic reactions seen with rocuronium & vecuronium

Anesthesiology.2015;122(1) AANA J.2012;80:129

Anesthetic Agents

- Latex
  - IgE – Ab to protein in natural rubber
  - see reaction 30 + minutes into case
    - rare on induction
  - gloves, drains, catheters
    - goal is to have a latex free operatory
- Chlorhexidine (Type I IgE reaction)
  - reports of anaphylaxis in urology & OB-GYN for catheters soaked in it
  - no reports for oral rinse
- Povidone-Iodine (Betadine)
  - anaphylaxis is rare
  - more contact dermatitis (Type IV cell mediated reaction)

Anesthetic Agents

- Antibiotics
  - penicillin & cephalosporins account for 70% of antibiotic anaphylaxis
  - vancomycin: usually not an allergic reaction
    - basophil mediated "red man syndrome" due to too rapid an infusion
  - quinolones
- Hypnotics
  - barbiturates: now just methohexital
    - IgE reactions
    - women > men
    - decreased use due to propofol
  - Propofol
    - "no contraindication" in egg, soy, or peanut allergy
      - may be wise to avoid use if there was anaphylaxis to these foods

Anesthetic Agents

- ketamine
  - any allergic reaction is rare let alone anaphylaxis
- etomidate
  - may be the most immunologically safe TIVA agent in use
  - do not worry about anaphylaxis
- benzodiazepines
  - allergic reactions are rare
- volatile anesthetic gases
  - no reports of anaphylaxis

Anesthetic Agents

- Opioids
  - life threatening reactions are rare
  - usually see pruritus, urticaria, & mild hypotension
  - *misinterpreted as allergic reaction*
    - direct action on mast cell for histamine release
    - rare to see any significant respiratory or CVS event
- Classes of Opioids
  - Natural opioids: morphine & codeine
  - Semi-synthetic opioids: oxycodone, hydrocodone, & hydromorphone
  - Diphenylheptanes: methadone & ~~propoxyphene (Darvon)~~
  - Phenylpiperidines: meperidine, fentanyl, sufentanil, remifentanil, & tramadol

Opioids

- Histamine release
  - Meperidine > morphine
  - histamine itching can be blocked by H1 and H2 histamine blockers
  - no proof that histamine release from opioids will induce bronchospasm
- Medical Clinics North America. 2010; 94: 761
  - 3 subclasses of opioids (based on cited article)
    - morphine – codeine
    - phenylpiperidines
    - methadone
    - *do not see cross reactivity* between the 3 subgroups
    - do see a cross sensitivity between morphine & codeine
    - do not see cross sensitivity between the phenylpiperidines

Anaesth Intensive Care.2012; 40: 216

Flushing, itching, hives, sweating, and/or mild hypotension only	Go to A
Itching, flushing, or hives at injection site	Go to A
Severe hypotension	Go to B
Skin reaction other than hive (e.g. rash)	Go to B
Breathing, speaking, or swallowing difficulties	Go to B
Angioedema	Go to B

- **Option A :** may be pseudoallergy from histamine: Drug options
  - nonopioid analgesic: tylenol or NSAID
  - avoid codeine, morphine, and meperidine
    - these are drugs commonly associated with pseudoallergy
  - use a more potent opioid less likely to release histamine
    - meperidine < codeine < morphine < hydrocodone < oxycodone < hydromorphone < fentanyl
  - add an antihistamine H1 and/or H2 blocker
  - dose reduction of opioid if tolerated

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Skin reaction other than hive (e.g. rash)	Go to B
Breathing, speaking, or swallowing difficulties	Go to B
Angioedema	Go to B

- Option B: may be true allergy: Drug options are
  - non opioid: NSAID or Tylenol
  - an opioid in different class from which patient reacted
    - need to monitor closely
    - tramadol is not an option for patients allergic to an opioid
    - codeine is not recommended due to poor efficacy
    - mild to moderate pain: NSAIDs are excellent option

www.prescriberletter.com accessed 5/2015

Opioids

- Reports in literature for anaphylactic reactions are rare
- How do you proceed if patient reports "allergic reaction"
- Should consult with allergist to
  - establish a definitive diagnosis
  - determine the need for desensitization
  - identify appropriate alternatives
- Cross sensitivity between classes is thought to be rare
  - data is limited
  - cross sensitivity is possible
  - proceed with caution
  - morphine should not cross react with fentanyl & its derivatives
  - apparent cross reactivity between fentanyl group

Clinical Reviews in Allergy. 1991;9:309

Management of Anaphylaxis

Epinephrine

- drug of choice for treatment of anaphylaxis
  - early use yields better outcomes
- benefits from use
  - ↓ mediator release from mast cells & basophils
  - prevents or reverses angioedema in upper airway
  - prevents or reverses bronchospasm
  - prevents or reverses CVS collapse
- not indicated in Grade 1 anaphylaxis
  - just skin reactions
  - antihistamines should work

Epinephrine

- α_1 adrenergic agonist
  - ↑ vasoconstriction & peripheral vascular resistance
  - ↓ mucosal edema
- β_1 adrenergic agonist
  - ↑ inotrope & chronotrope
- β_2 adrenergic agonist
  - ↑ bronchodilation
  - ↓ mediator release from mast cells & basophils

Epinephrine

- IM dose is preferred to SQ route & safer than IV route
- IM in thigh (vastus lateralis) is absorbed better than arm (deltoid)
- Adult dose: 0.01 mg/kg 0.3 mg to 0.5 mg IM
  - repeat doses Q 5 to 15 mins
  - most cases respond to single dose of epinephrine
  - may need second dose → rare to need 3rd
  - auto injector dose in adult = 0.3 mg IM
- Child dose: 0.01 mg/kg maximum dose = 0.5 mg
  - auto injector dose in child = 0.15 mg

Anesth Analg.2008;107:620

IV Dose Epinephrine

- Grade 1 anaphylaxis: not indicated
- Grade 2 anaphylaxis: 10 to 20 mcg IV
- Grade 3 anaphylaxis: 100 to 200 mcg IV
  - may repeat Q 1 to 2 minutes
- Grade 4 anaphylaxis: cardiac arrest
  - 1 mg IV Q 5 minutes
- IV dose has multiple cardiac side effects
  - not indicated unless multiple IM injections have failed
  - patient is still hypotensive after fluids & IM epinephrine
  - dose should be 50 to 100 mcg IV

J All Clin Immun Pract. 2015; January issue

IV Epinephrine

- 1: 1000 epinephrine 1ml = 1 mg
- Dilution for intravenous use
  - TB syringe: draw 0.1 ml from the 1: 1000
  - 0.1 ml = 100 mcg
  - dilute this 0.1 mg to full 1 ml in syringe
  - now have 10 mcg per 0.1 ml
- 1: 1000 epinephrine 1ml = 1 mg = 1000 mcg
  - add 1000 mcg to 100 ml of saline
  - now have 100 mcg per ml
  - take 1 ml (100 mcg/ml) and dilute in syringe to 10 ml
  - now have 10 mcg per ml
- 1: 1000 epinephrine: add 1 mg to 250 ml or 500 ml bag
  - get 4 mcg per ml or 2 mcg per ml respectively

Refractory Hypotension

- patients on beta blockers can be resistant to the vasopressors
- develop refractory hypotension & bradycardia
- glucagon is useful in these cases
- Glucagon
  - acts independent of the beta adrenergic system
    - get ↑ in cyclic AMP
      - cAMP causes muscle contractions
  - ↑ inotropic & chronotropic effects of heart
  - initial dose = 1 to 5 mg then start infusion
    - infusion 1 to 2.5 mg/hr.
  - rapid bolus = N/V
  - COST: 1 mg emergency kit (2 kits = $400 to $420)

Refractory Hypotension

- Vasopressin
  - non adrenergic vasoconstrictor
  - can enhance the effects of an adrenergic agonist
  - drug activates vascular V_1 receptors
    - causes vasoconstriction
  - reported use in anaphylaxis
    - will cause vasoconstriction in skin, skeletal muscle, intestines, and fat
    - problematic side effect
      - vasoconstriction in coronary vessels
      - decrease in cardiac output
  - dose is 4 Units for a 70 kg patient 0.06 U/kg IV
  - infrequently used

Anest Analg. 2008;107:620-4

Vasopressin

- Shortage of generic vasopressin
  - may not come back
  - 20 Unit/ml vials
    - 25 vials for $190 to $195
    - 5 vials for $84
- Brand name newly released = VASOSTRICT
  - 20 Units/ml $58.79 per vial

IV Fluids

- anaphylaxis
  - lose 35 to 50% of intravascular volume in 10 mins
  - need fluids to support perfusion & BP
- adults
  - NSS 1 to 2 L rapid infusion
    - 10 to 25 ml/kg over 2 minutes
      - another source: 5 to 10 ml/kg in 1st 5 minutes
    - repeat as needed to support BP
    - after exceed 30 ml/kg switch to colloids
- children
  - 20 ml/kg bolus NSS repeat as needed

AANA J. 2012;80:129 UptoDate 2015

Albuterol for Bronchospasm

- MDI albuterol for bronchospasm
  - adapters for ET tube
  - open airway general anesthetics
    - how do you get it to lungs and not just in the pharynx?
- albuterol nebulizer with face mask
- IV albuterol unavailable in office

Glucocorticoids

- will not relieve initial symptoms in anaphylaxis
  - take several hours to reach an effect
- may prevent biphasic or protracted anaphylaxis
  - no proof
  - just a preventive measure
- hydrocortisone will have fastest onset

- Adult dose
  - hydrocortisone 1 to 2.5 mg/kg IV (250 mg IV)
  - methylprednisolone 1 mg/kg IV (80 mg IV)

- Child dose
  - hydrocortisone 50 to 100 mg IV
  - methylprednisolone 2 mg/kg IV

Post Anaphylaxis

- Laboratory tests to confirm diagnosis
  - tryptase levels: draw during acute episode
    - wait at least 15 minutes into attack but before 3 hours
  - histamine levels: draw during attack
    - have between 5 to 15 minutes to get a level

- Refer to allergist for testing in 4 to 6 weeks

Hereditary Angioedema

Hereditary Angioedema

- 1888: described as hereditary angioneurotic edema
- 1963: genetic mutation in C1 Inhibitor enzyme
  - chromosome 11q12-q13.1.15
- autosomal dominant inheritance
  - 25% cases occur de novo
  - no ethnic preference
  - males = females

- recurrent episodes of angioedema without urticaria or pruritus
  - usually a slow onset over 24 hours → some cases develop rapidly
  - resolves in 48 to 72 hours

- deficient or dysfunctional C1 esterase inhibitor (C1-INH)

Hereditary Angioedema

- subcutaneous & submucosal lesions
  - usually acute swelling → isolated to 1 specific area but it can spread

- larynx & pharynx: potentially life threatening

- GI – abdominal lesions account for 50% of cases
  - pain, bowel distention, nausea, vomiting, & diarrhea
- incidence: 1:50,000 (range 1:10,000 to 1:150,000)
  - approximately 6000 patients in US
- onset
  - 40% cases occur before age 5
  - 75% cases occur ≥ age 15
  - episodes increase in frequency after puberty
  - rare to see multiple episodes prior to puberty

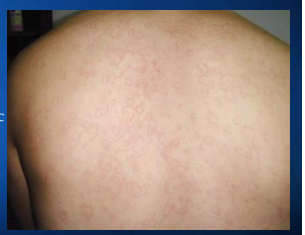
Hereditary Angioedema

- Bork 2006 review
  - 195 patients with HAE
  - 54% had on average → more than 12 attacks per year
  - Symptom free years were rare → 370 (6.5%) of the 5736 patient-years included in the study

Am J Med.2006;119:267

Prodromal Signs

- several days prior to onset of swelling
  - fatigue
  - nausea
  - abdominal distention
  - tingling & burning
- erythema marginatum
  - raised, serpiginous, non pruritic rash on trunk, arms, or legs
  - not see on face
  - "looks like chicken wire"



Clinical Features Cutaneous Lesion

- location → extremities, face, & genitalia
- non pitting edema
- no urticaria or pruritus
- disfiguring swelling
  - painful → may require use of opioids
  - dysfunction → unable to use hands → difficult to walk
- prior to swelling may report tingling sensation
  - swelling develops over the next 2 to 3 hours
  - subsides in 48 to 72 hours

Laryngeal Angioedema

- laryngeal angioedema
  - can be isolated swelling to larynx
  - can result from extension from lips, tongue, floor of mouth, uvula, or palatal swelling
- 50% of patients have at least 1 episode in lifetime
- dental interventions will increase the risk
  - especially oral surgical procedures
- majority of cases occur between the ages of 11 to 45 yrs.
- usually develops over the course of several hours
  - mean time = 7 hours
  - can occur in just a few minutes
  - many attacks regress spontaneously without airway compromise
  - deaths hours after dental appointment at home secondary to edema

Laryngeal Angioedema

- Predyspnea Phase
  - average duration is 3.7 hours
  - range is 0 to 11 hours
  - sensation of lump in throat, tightness in throat, or dysphagia
- Dyspnea Phase
  - laryngeal edema has developed
  - average time from dyspnea to complete upper airway obstruction & loss of consciousness → 41 minutes
    - range is 2 minutes to 4 hours
- LOC Phase
  - loss of airway → death within 9 minutes
  - range of 2 to 20 minutes
- ***Cases demand a low threshold for intubation***

Triggers

- traumatic injuries account for 50 to 54% of cases
  - dentistry especially surgery → even injections of local anesthesia
    - case report secondary to dental impressions
  - intubation
  - tongue piercings
- sexual intercourse → genital swelling
  - riding horses or bicycles as well
- emotional stress
- infections
- medications
  - BCP & estrogen replacement therapy
  - Tamoxifen
  - ACE inhibitors

Vasopressor in Local Anesthetics

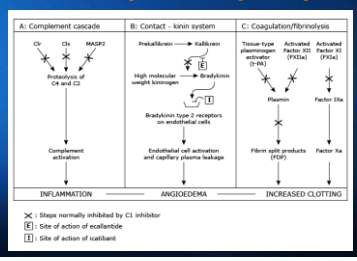
- epinephrine in local anesthesia
  - epinephrine can cause release of vasopressin
  - vasopressin activates Factor XII to Factor XII_a
  - get release of bradykinin to increase vasodilation & edema
  - develop angioedema in patients with HAE
- felypressin found in local can also do the same
- avoid vasoconstrictor in local anesthesia
- *referenced in a single source → no other*
  - *JOMS. 2014;72: 2421*

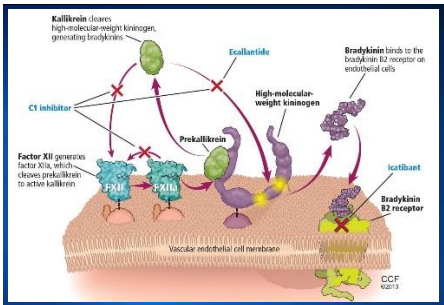
Pathophysiology of HAE

- C1 inhibitor (C1-INH) → normal function
  - prevents excessive vascular permeability by regulating
    - classical complement pathway
    - fibrinolytic pathway
    - coagulation pathway
    - kallikrein – kinin contact pathway (KKS pathway)
  - role in classical complement
    - inactivates C1r, C1s, C2, and C4 to prevent ↑ in vasodilation & vascular permeability
  - role in contact pathway
    - regulates inhibition of kallikrein
  - role in coagulation pathway
    - inhibits activation of Factor XII

Physiology of C1 Inhibitor

- C1 inhibitor → 2 most important clinical roles
  - inhibits the conversion of prekallikrein to kallikrein
    - by preventing activation of Factor XII
  - inhibits kallikrein breakdown of high molecular weight kininogen to bradykinin





Cleve Clinic. 2013; 80(5): 297-308

- Tissue trauma activates Factor XII
- C1 INH limits activation of Factor XII & formation of kallikrein
  - prevents additional activation of Factor XII
  - limits the amount of bradykinin that is produced

Pathophysiology of HAE

- angioedema is the result of deficient or dysfunctional C1 inhibitor
- acute HAE see over activation of kallikrein-kinin contact system
- get ↑ bradykinin levels
  - in acute attack → levels are 7 times normal
- bradykinin bonds to bradykinin B2 receptor
  - ↑ in vasodilation
  - ↑ in vascular permeability
  - ↑ in extravasation of plasma into submucosal or subcutaneous compartments

Types of HAE

- Type I
  - 85% of HAE cases
  - 75% cases have family history
  - low levels of C1-INH
    - levels 10 to 30% of normal
  - onset childhood – young adult
    - worsening after puberty
- Type II
  - 15% of cases
  - 75% cases have family history
  - dysfunctional C1-INH
  - onset childhood – young adult
    - worsening after puberty

Types of HAE

- Type III HAE
  - normal level of C1-INH
  - HAE-XII subtype
    - women → may be estrogen dependent
    - mutation in gene for Factor XII
  - typical onset after childhood
  - face, tongue, extremities more common than abdominal
    - recurrent episodes of tongue swelling frequent
  - more disease free periods than Type I or II
  - family history same as Type I and II
- Type I, II, III
  - will not respond to antihistamines, corticosteroids, or epinephrine

Laboratory Testing

	C4 Level	C1-INH Level	C1-INH Function
Type I HAE	Low	Low	Low < 50% normal
Type II HAE	Low	Low or elevated	Low < 50% normal
Type III HAE	Normal	Normal	Normal

- referral to allergist – internist
- initial screening labs: C4, C1-INH antigenic level, & C1-INH functional level
- additional testing: C1q & C3 levels
- genetic testing usually unnecessary in adults
  - value in children

Testing Summary

Angiodema disorder	C4*	C1 inhibitor level	C1 inhibitor function	C1q	C3	Other tests (not routinely needed for diagnosis)
HAE I	Low	Low	Low (usually <50 percent of normal)	Normal	Normal	Genetic testing
HAE II	Low	Normal or elevated	Low (usually <50 percent of normal)	Normal	Normal	Genetic testing
HAE III	Normal	Normal	Normal	Normal	Normal	Mutations in gene for factor XII detected in some patients

UptoDate: Accessed Jan 2015

Agents Used to Manage HAE

C1-INH Replacement Therapy

- plasma derived C1-INH concentrate (Berinert)
  - nanofiltered, lyophilized, & pasteurized pooled product
  - replenishes low C1 esterase inhibitor levels
  - approved by FDA 2009 (Vial 500 Units add 10 ml water)
  - dose = 20 Units/kg IV for acute HAE
    - 1000 U IV weight based dose ≤ 50 kg
    - 1500 U IV weight 51 to 100 kg
    - 2000 U IV weight > 100 kg
  - can be self administered
  - resolve acute attack 30 to 60 minutes
  - raises C1 INH levels by > 50% in 30 minutes
    - maintains levels for 3 to 4 days

C1-INH Replacement Therapy

- 5% patients need re-dosed in an acute attack
  - 2nd dose in 2 hours if symptoms persist
  - if symptoms worsen → give 2nd dose 30 minutes after 1st dose
- onset of relief
  - laryngeal edema 26.4 minutes
  - facial edema 28.8 minutes
  - extremities 25.8 minutes

  Onset is ~ 30 minutes
- complete resolution
  - laryngeal edema 5.8 hours
  - facial edema 26.6 hours
  - extremities 22.7 hours
- side effects: unusual but include headache & fever
- COST: 500 Units $2600 per vial (Jan 2015)

Recombinant C1 INH Therapy

- recombinant human C1INH (Ruconest)
- shorter half life than pdC1INH
- dose = 50 Units/kg IV
  - 1 vial IV for patients < 84 kg
  - 2 vials IV if > 84 kg (4200 Units)
  - maximum daily dose = 4200 Units
- FDA approved 2014
- rare to redose --- relapse is rare
- side effects: HA, N/V, diarrhea
- anaphylactic reaction in rabbit sensitized patients

Icatibant (Firazyr)

- synthetic bradykinin receptor – 2 antagonist
- 2011 FDA approved for patients ≥ 18 years old

- dose = 30 mg SQ
  - additional doses: 30 mg SQ Q 6 h as needed
  - maximum dose: 90 mg in 24 hours
  - 30 mg in 3 mls of fluid → painful injection
- can be self administered
- no anaphylaxis
- side effects: pain on injection, nausea, HA, fever
- laryngeal edema: 50% reduction in 2.5 hours
  - in one study: no patient needed airway rescue during that time
- COST: $8000 to $8700 for 1 vial (Jan 2015)

Ecallantide (Kalbitor)

- genetically engineered recombinant plasma kallikrein inhibitor
  - inhibits breakdown of high molecular weight kininogen to bradykinin

- FDA approved in 2009 for acute HAE patients ≥ age 16
- dose = 30 mg SQ (Vial is 10 mg in 1 ml fluid)
  - give in 3 separate sites separated by 2.5 cm
  - 2nd dose of 30 mg if needed → 1 hour after 1st dose or as needed over the next 24 hours

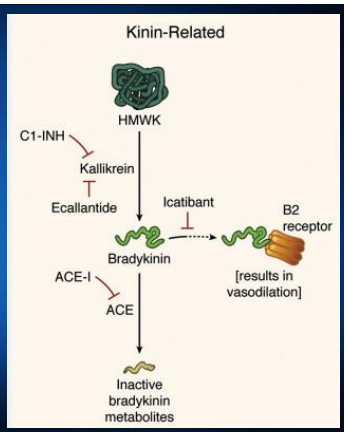
- anaphylaxis risk: 2.7% patients in 1st hour
  - can not self administer drug

- side effects: HA, nausea, fatigue, and diarrhea
- COST: Vial 10 mg (3 vials = $11,300 to 12,000) Jan 2015

Ecallantide prevents breakdown of HMWK to bradykinin

Icatibant prevents bradykinin from binding to B2 Receptor

C 1 Inhibitor Replacement prevents formation of kallikrein



Product Cost and Availability

Medication	Strength	Package size	AGH Acquisition Cost	Typical Dose	Price per Dose
Icatibant (Firazyr ®)	10 mg/ml	3 ml x3	22,896.86	30 mg	7,632.29
	10 mg/ml	3 ml x1	7,632.29		
C1 Esterase Inhibitor (*Cinryze™*)	500 units	500 unitsx1	2,576.40	1000 units	5,152.80
C1 Esterase Inhibitor (*Berinert®*)	500 units	500 unitsx1	1,870.52	20 units/kg	7,482.08
Ecallantide (*Kalbitor®*)	10 mg/ml	10 mg x3	11,241.30	30 mg	11,241.30

Hospital Cost

Medications for acute attacks of hereditary angioedema

Drug	Approved	Self-dosing	Dosage	Potential adverse effects
Plasma-derived nanofiltered C1 inhibitor (Berinert)	United States: adolescents and adults Europe: all ages	Yes	20 U/kg intravenously	Rare: anaphylaxis Theoretical: blood-borne infection
Plasma-derived nanofiltered C1 inhibitor (Cinryze, Cetor)	Europe: adolescents and adults	Yes	1,000 U intravenously, with possibility of second dose of 1,000 U after 60 minutes	Rare: anaphylaxis Theoretical: blood-borne infection
Ecallantide (Kalbitor)	United States: ≥ 16 years old	No	30 mg subcutaneously	Uncommon: antidrug antibodies, anaphylaxis
Icatibant (Firazyr)	United States and Europe: ≥ 18 years old	Yes	30 mg subcutaneously	Common: transient discomfort at injection site
Recombinant human C1 inhibitor (Rhucin)	Europe: adults United States: pending	No	50 U/kg or 4,200 U intravenously, whichever dose is higher	Uncommon: anaphylaxis in rabbit-sensitized patients

Cinryze is FDA approved for prophylaxis

Management of Acute HAE

- Laryngeal Edema
  - most dangerous acute attack
  - usually progresses over several hours
    - sometimes onset is rapid
  - intubation becomes difficult as airway distorts from edema
  - none of the available treatments are universally effective
    - variable onset & resolution times
  - *must have a low threshold to intubate*
    - avoid blind nasal if possible → may induce additional trauma
    - avoid LMA → wide contact area of mask can traumatize tissue
      - does not prevent additional swelling

- initiate appropriate drug therapy
  - C1INH replacement, icatibant, or ecallantide are all 1st line agents

Short Term Prophylaxis

- Minor Procedures
  - injection of local anesthesia, cleanings, & restorative care
  - pdC1INH (plasma derived C1INH) is immediately available
    - no previous attacks under similar care
      - no prophylaxis is necessary
  - pdC1INH unavailable
    - anabolic androgen (Danazol) 2.5 mg/kg/day PO
      - maximum dose of 600 mg/day
      - 5 days before → 2 to 5 days after procedure
    - stanozolol 4 to 6 mg/day is an alternative
  - tranexamic acid 20 to 50 mg/kg/day PO split BID or TID
    - 3 to 6 grams/day maximum

Short Term Prophylaxis

- Major procedures or intubation
  - pdC1INH (plasma derived C1INH) available
    - 10 to 20 Units/kg IV 1 hour before procedure
    - need to have 2nd dose available
  - pdC1INH not available
    - danazol as per minor procedures
    - androgens are preferred over tranexamic acid
    - FFP in addition to danazol
      - can exacerbate an episode of HAE instead of preventing it
        - transfusion of complement factors to increase edema
      - FFP 10 ml/kg or 2 to 4 units for an adult
      - repeat Q 2 to 4 hours

Allergy, Asthma, & Clin Immun. 2010;6:24

Current Short Term Prophylaxis

- As of 2014
  - do not rely on androgens, tranexamic acid, of FFP
  - pdC1INH, recombinant C1INH, ecallantide, & icatibant
- Minor procedures → no prophylaxis if above available
- Major procedures or intubation
  - consider use of all 4 for maximum protection
  - pdC1INH 10 to 20 U/kg IV + ecallantide 30 mg SQ
    - 1 to 6 hours before surgery
  - icatibant 30 mg SQ 30 minutes before surgery or ET tube
  - additional doses of pdC1INH as needed for reactions
- $$$$$$$$

J Clin Anesth. 2013; 25: 335-343

Prophylaxis for Dental Procedures

- historically → overall mortality after dental procedures without prophylaxis → 30 to 40%
- Bork et al: 171 HAE patients → 801 extractions
  - 62.8% patients and 78.5% extractions without prophylaxis
    - no acute HAE attack
  - 37.2% patients and 21.5% extractions with prophylaxis
    - had isolated facial edema, isolated laryngeal edema, or both
    - prophylaxis was with pdC1-INH concentrate

Table III. Number of hereditary angioedema (HAE) attacks according to body site after tooth extraction with and without short-term prophylaxis with C1 inhibitor concentrate

Patients	*No. of tooth extractions*	*No. of HAE attacks*	*Facial edema (isolated)*	*Laryngeal edema (isolated)*	*Both facial and laryngeal edema*
Prophylaxis with 500 U	75	12	8	3	1
Prophylaxis with 1000 U	53	4	1	1	2
Total with prophylaxis	128	16	9	4	3
Without prophylaxis	577	124	88	8	28

OOO.2011;112:58-64

Prophylaxis for Dental Procedures

- mean time between extractions and onset of HAE symptoms
  - 8.4 hours (with a range of 4 to 36 hours)[1]
  - report of laryngeal edema in as short as 20 minutes[2]
- many of the attacks occur within 12 hours of extractions
  - high risk of an attack at night while asleep
  - 4 cases in 2003: fatal edema at night while asleep after extractions[3]
- prophylaxis cannot completely eliminate the risk
  - acute treatment medications need to be available[4]

OOO.2011;112:58 [1] J Investig Allergol Clin Imm.2013;23:1 [2,4] JADA.2003;134:1088 [3]

Prophylaxis for Dental Procedures

- currently most case reports use pdC1-INH concentrate for prophylaxis
  - should keep levels up for 1 to 2 days
- short term prophylaxis should be given to all HAE patients prior to dental procedures[4]
  - consult with allergist: give agent of just have on hand
  - depends on patient, procedure, and history of reactions
- patients need to have a supply of agent for discharge use at home
- is costly treatment

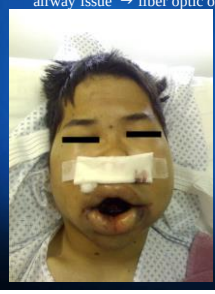
OOO.2011;112:58 [1] J Investig Allergol Clin Imm.2013;23:1 [2,4] JADA.2003;134:1088 [3]

Medications for prophylaxis of hereditary angioedema

Drug	Approved	Self-dosing	Dosage	Potential adverse effects
Plasma-derived nanofiltered C1 inhibitor (Cinryze)	United States and Europe: ≥ 12 years old	Yes	Short-term: 500–1,500 U intravenously 1 hour before event Long-term: 1,000 U every 3–4 days	Rare: anaphylaxis Theoretical: blood-borne infection
Danazol (Danocrine)	United States: adults Contraindicated during pregnancy and lactation, children until growth is complete	Yes	Short-term: 200 mg by mouth 3 times a day for 5–10 days before event Long-term, adult: ≤ 200 mg/day (100 mg every 3 days–600 mg/day) Children: 50 mg/day (50 mg/week–200 mg/day)	Common: Weight gain, virilization, acne, altered libido, muscle pains and cramps, headaches, depression, fatigue, nausea, constipation, menstrual abnormalities, elevated liver enzymes, hypertension, alterations in lipid profile Uncommon: decreased growth rate in children, masculinization of female fetus, cholestatic jaundice, peliosis hepatis, and hepatocellular adenoma and carcinoma
Aminocaproic acid (Amicar)	Not approved for hereditary angioedema	Yes	Adults: 1 g by mouth 3 times daily Children: 0.05 g/kg twice daily (0.025 g/kg twice daily–0.1 g/kg twice daily)	Common: nausea, vertigo, diarrhea, postural hypotension, fatigue, muscle cramps with elevated muscle enzymes Uncommon: thrombosis
Tranexamic acid (Lysteda)	Not approved for hereditary angioedema	Yes	Adults: 1 g twice daily (0.25 g twice daily–1.5 g three times daily) Children: 20 mg/kg twice daily (10 mg/kg twice daily–25 mg/kg 3 times daily)	Same as with aminocaproic acid

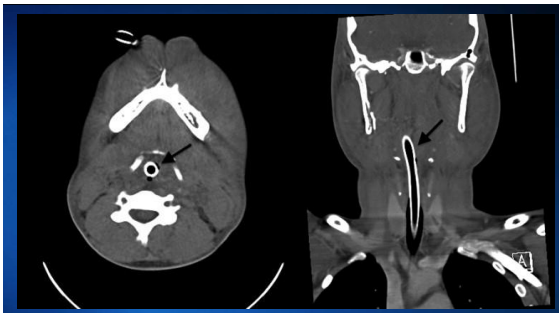
Oral Surgery

- 18 yr old male for LeFort I and BSSRO mandible
  - 24 hours post op → facial edema that kept increasing presenting with airway issue → fiber optic oral intubation



Facial swelling secondary to surgery along with angioedema of the lips and airway

JOMS.2013;71:e185-e188



Oral ET tube is completely surrounded by laryngeal – pharyngeal edema.

If intubation were delayed, the patient would require a surgical airway.

Management

- secure airway
- is this just unusual post surgical edema?
- is this an allergic reaction?
  - allergy history in patient
  - more than 24 hours post op → unlikely to be anaphylaxis
  - clearly is angioedema → unlikely to be allergic in nature
    - it is 24 hours after surgery
    - slow onset
  - consider dose of epinephrine & antihistamines → "knee jerk rxn"
    - was given without any decrease in swelling
- draw labs
  - C4 & C1 INH levels
  - ask family about any similar episodes from any trauma?

Management

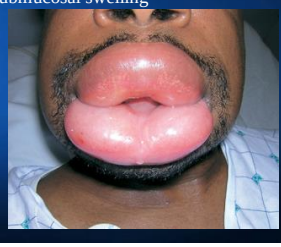
- C4 level was low & C1-INH was low normal
- Family reports an episode of angioedema from extractions in past

- Supports diagnosis of HAE
  - get allergy consult
  - treat with pdC1-INH concentrate, ecallantide, or icatibant
  - in this case they used FFP 2 Units
    - 10% reduction in 12 hours
    - extubated after 24 hours
    - FFP is no longer a 1st line agent in HAE

JOMS. 2013;71:e185

ACE-Inhibitor Angioedema

- 0.1 to 0.68% incidence with ACE inhibitors
- 0.1 to 0.4% incidence with ARB agents
- 3X more common in Blacks
- accounts for 20 to 40% of angioedema ER visits
- non pitting subcutaneous or submucosal swelling
- other risk factors
  - female > male
  - age > 65
  - smoker
  - history of ACE-I cough



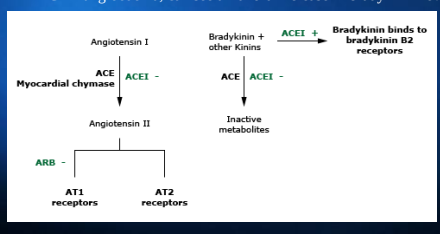
Curr Opin Anesthesiol.2012:25:1

Clinical Features

- most cases present as swelling of lips, tongue, or face
- occasional episodes of intestinal swelling
- may involve pharynx & larynx
  - 10% incidence of UAO
- will not see pruritus or urticaria
- swelling develops in minutes to hours
- resolves in 24 to 72 hours
- 50% cases occur during the 1st week of drug use
- 66% occur within 3 months
- sometimes it will take years before you see angioedema

Angiotensin Converting Enzyme

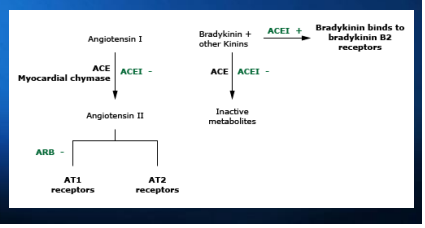
- converts angiotensin I to angiotension II
  - angiotensin II causes vasoconstriction
- ACE is also a kininase enzyme
  - prevents bradykinin formation
  - in ACE-I angioedema, can see a 10 fold increase in bradykinin levels



Angiotensin Receptor Blockers

- ARBs selectively inhibit AT1 receptors
  - 3 to 3.7 fold increase in Angiotensin I levels
  - 2 to 2.5 fold increase in Angiotension II levels
  - 2 fold increase in Bradykinin levels
  - AT2 receptors are activated to increase kinin levels and stimulate B2 receptors

Expect to see increase in angioedema



Treatment for ACEI Angioedema

- Airway is top priority
- Stop the drug
  - reactions will resolve even if you don't stop the drug → just takes longer to resolve
- Antihistamines, corticosteroids, and epinephrine
  - typically will not work
  - not a mast cell mediated response
  - not unusual to see them being used → in "heat of battle" trying to rule out an anaphylactic reaction

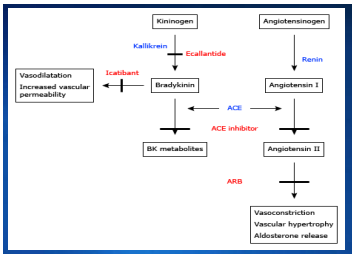
Renin – Angiotensin – Aldosterone - System (RAAS) Inhibitor Induced Angioedema

Angioedema Type	Clinical Features	Management	Treatment
Mild (Type I)	Face, lips, & anterior tongue	Observe in ER or regular floor	Corticosteroids & Antihistamines
Moderate (Type II)	Edema extended to base of tongue, floor of mouth, soft palate, and uvula	Admit to ICU	Add Epinephrine for stridor
			Add FFP
			Add Icatibant or other HAE agents
Severe (Type III)	Supraglottic & laryngeal edema	Admit to ICU	Use Type I & II treatments
	Drooling, hoarseness, or dyspnea		Intubate

Curr Opin Anesthesiol. 2012: 25(3): 356

Severe Cases of ACEI Angioedema

- Severe cases: Laryngeal edema & UAO
  - icatibant: bradykinin B2 receptor antagonist
    - has been successful → symptoms have improved
  - ecallantide: prevents breakdown of HMW kininogen to bradykinin
  - FFP: there is angiotensin converting enzyme in FFP
    - will reverse ACEI angioedema → has worked
    - 2 Units in adults
  - pdC1INH concentrate: has also been effective



Blue = enzymes
Red = drugs

ACE-I or ARB Induced Angioedema Treatment
Discontinue the offending agent
Epinephrine, corticosteroids, & antihistamines → effectiveness is unproven but still used → want to rule out allergy
Literature reports to date: FFP, pdC1-INH concentrate, & icatibant have been successful in reversal

ACE-I & ARB Agents and HAE

- HAE Type I & II
  - majority of HAE cases
  - complement pathway is involved → C4 levels are low
  - low functional C1-INH levels
- ACE-I & ARB angioedema
  - C4 levels are normal as is the level of functional C1-INH
  - FFP has been shown to improve ACE-I angioedema
    - not recommended for HAE Type I or II
- ACE-I do not seem to exacerbate angioedema in HAE patients
  - caution for use in HAE patients is still wise
- Use of ARBs in patients who have ACE-I angioedema
  - only in cases where benefit clearly outweighs the risk

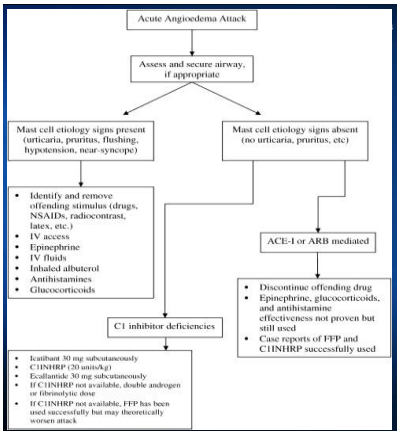
Cleve Clin J Med. 2013;80:755

Complement profiles in angioedema syndromes

	C4 level	Antigenic C1 inhibitor level	Functional C1 inhibitor level	C1q level	C3 level
Hereditary angioedema types I and II	Low	Low (type I) Normal (type II)	Low (both types I and II)	Normal	Normal
Hereditary angioedema type III	Normal	Normal	Normal	Normal	Normal
Acquired C1 inhibitor deficiency	Low	Low	Low	Low	Normal
Allergic angioedema	Normal	Normal	Normal	Normal	Normal
ACE-inhibitor-associated angioedema	Normal	Normal	Normal	Normal	Normal
NSAID-associated angioedema	Normal	Normal	Normal	Normal	Normal
Idiopathic angioedema	Normal	Normal	Normal	Normal	Normal
Angioedema with urticarial vasculitis	Low	Normal	Normal	Low	Low

ACE = angiotensin-converting enzyme; NSAID = nonsteroidal anti-inflammatory drug

Cleve Clinic Med. 2013;80:297



ACE-I is ACE inhibitor

ARB is angiotensin receptor blocker

FFP= fresh frozen plasma

HAE drugs: Icatibant, Ecallantide, & C1-INH pooled plasma concentrate

J Clin Anesth.2013;25: 335

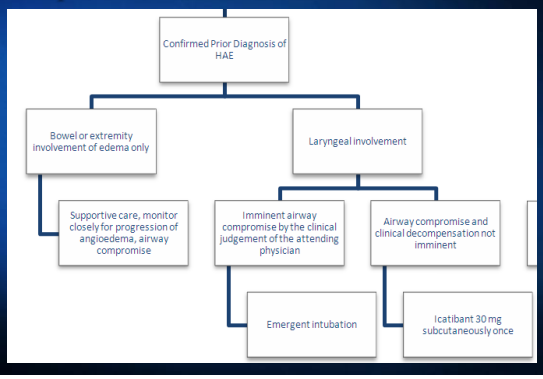
Proposed Guidelines for Angioedema with Urticaria

Associated urticaria, no ACE-inhibitor use history, no confirmed prior diagnosis of HAE

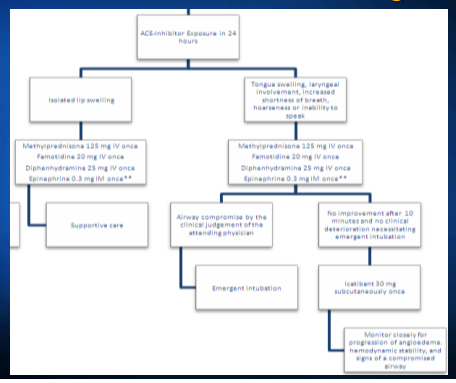
Methylprednisolone 125 mg IV once
Famotidine 20 mg IV once
Diphenhydramine 25 mg IV once
Epinephrine 0.3 mg IM once**

** At the discretion of the attending physician based upon vital signs and clinical presentation

Proposed Guidelines for Use in HAE



Proposed Guidelines for ACE-Induced Angioedema



Local Anesthesia & Allergy

- Incidence of allergy is rare < 1%
- 2 types of reactions reported
  - contact dermatitis at site
  - urticaria, angioedema, or anaphylaxis
- Localized Swelling or Contact Dermatitis
  - eczematous and pruritic rash at site of administration
  - vesiculation, blistering, or weeping
  - mucosal blisters which slough
  - delayed reaction up to 72 hours after exposure
  - refer to allergist for Patch Testing on skin
  - cross reactivity occur in each group but usually not between groups

Local Anesthesia & Allergy

- 2 Groups of local agents
  - Group I = esters
    - benzocaine & procaine
  - Group II = amides
    - lidocaine, mepivicaine, articaine, prilocaine, & bupivacaine
- Uritcaria, angioedema, and anphylaxia
  - rare for local anesthesia
  - case reports for lidocaine & articaine
  - positive skin testing reported for
    - lidocaine, articaine, mepivicaine, & bupivacaine
  - may not identify drug specific IgE in blood

Local Anesthesia & Allergy

- Cross Reactivity
  - evidence for cross reactivity between amides
  - lack of evidence for cross reactivity between esters and amides
- Skin testing
  - skin prick test with undiluted agents is typically 1st test & if negative proceed with intradermal
  - intracutaneous (intradermal) skin testing with 1:100 dilution
    - no false positives with this concentration
  - a positive skin test should be interpreted as a possible allergy

Negative Skin Test

- Negative test is not absolute proof of no allergy….. however
  - negative test is predictive of tolerance to local on challenge
- Challenge test is recommended because false negatives are rare but possible
  - Upper lateral arm for subcutaneous injection of undiluted local in increasing volumes (0.1, 0.5, 1.0 ml of local)
- Positive Challenge: reaction within 20 minutes
  - urticaria at injection site
  - acute onset rash distant from the site
  - 15% decrease in BP or pulmonary function
  - wheeze
  - Avoid use of that agent in patient

Negative Challenge

- Patient should not be at risk for an immediate allergic reaction
  - anaphylaxis should not occur
  - unlikely to see any immediate reaction
  - any reaction seen unlikely to be IgE reaction
- Need skin testing + challenge testing by allergist
  - do not give carpule with vasoconstrictor for test (Plain local)
  - vasoconstrictor has sulfites as preservative
  - list all contents of carpule for allergist
- 1% diphenhydramine as local anesthetic
  - infiltration or block duration of 30 minutes
  - 1 to 4 ml Maximum dose 50 mg
  - burning, erthyema, & swelling side effects

Thank you
Any Questions?

Edward C. Adlesic, DMD
Oral and Maxillofacial Surgery
Pittsburgh, Pa
edward_adlesic@msn.com