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

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
Immediate Allergic Reactions

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 re-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

Urticaria (Hives)

- transient blanchable, 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

Can measure some of the mediators to define the type of reaction
Management: Antihistamines

- **H₁ 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)

- **H₂ 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

- **GI & CVS:** 30% cases
  - N/V, diarrhea, & abdominal pain
  - dizziness, syncope, hypotension, & tachycardia

- **Upper airway:** 20% cases
  - tongue & laryngeal edema

- “**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

Grading Perioperative Anaphylaxis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Cutaneous Signs only</td>
<td>Erythema, angioedema, &amp; urticaria</td>
</tr>
<tr>
<td>II</td>
<td>Mild Systemic Reaction</td>
<td>Cutaneous Signs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CVS: Hypotension &amp; Tachycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Respiratory: wheeze &amp; dyspnea</td>
</tr>
<tr>
<td>III</td>
<td>Life-threatening</td>
<td>CVS collapse, tachycardia or bradycardia, &amp; dysrhythmias</td>
</tr>
<tr>
<td>IV</td>
<td>Cardiac Arrest</td>
<td></td>
</tr>
</tbody>
</table>

Anesth Analg, 2015; 121: 117

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.

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

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: 609-710
Perioperative Anaphylaxis

- 1:5000 to 1:20,000 anesthetics
  - IgE anaphylaxis: 80% 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

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)

Anesthesia: induction medications or antibiotic

- See hypotension, tachycardia, wheeze, or ventilation difficulty
- Think anaphylaxis

Perioperative Anaphylaxis

Agents Causing Perioperative Anaphylaxis

<table>
<thead>
<tr>
<th>Agent</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMBA</td>
<td>58%</td>
<td>70%</td>
<td>62%</td>
<td>23%</td>
</tr>
<tr>
<td>Anesthetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>15.1%</td>
<td>15%</td>
<td>4.7%</td>
<td>59%</td>
</tr>
<tr>
<td>Latex</td>
<td>16%</td>
<td>23.3%</td>
<td>16.5%</td>
<td>18%</td>
</tr>
<tr>
<td>Opioids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

UptoDate Accessed Jan 2015

Here: increase in end tidal CO$_2$; other sources decrease in end tidal CO$_2$
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 > vecuronium > atracurium > vecuronium
    - 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 vecuronium & 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

- 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 (Darvocet)
  - Phenylpiperidines: meperidine, fentanyl, sufentanil, remifentanil, & tramadol

- **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**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Go to</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itching, flushing, or hives at injection site</td>
<td>A</td>
</tr>
<tr>
<td>Severe hypotension</td>
<td>B</td>
</tr>
<tr>
<td>Skin reaction other than hive (e.g. rash)</td>
<td>B</td>
</tr>
<tr>
<td>Breathing, speaking, or swallowing difficulties</td>
<td>B</td>
</tr>
<tr>
<td>Angioedema</td>
<td>B</td>
</tr>
</tbody>
</table>

- **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 (order of histamine release)
  - Add an antihistamine: H1 and/or H2 blocker
  - Dose reduction of opioid if tolerated

- **Option B:** may be true allergy: Drug options are
  - Non opioid: NSAID or Tylenol
  - An opioid in a 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

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

- $\alpha_1$ adrenergic agonist
  - $\uparrow$ vasoconstriction & peripheral vascular resistance
  - $\downarrow$ mucosal edema
- $\beta_1$ adrenergic agonist
  - $\uparrow$ inotrope & chronotrope
- $\beta_2$ adrenergic agonist
  - $\uparrow$ bronchodilation
  - $\downarrow$ 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 (deltoïd)

- 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 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

Refactory 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
  - ↑ 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 $387.21
Vasopressin
- non adrenergic vasoconstrictor
- can enhance the effects of an adrenergic agonist
- drug activates vascular V1 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:S20-4

Shortage of generic vasopressin
- may not come back
- 20 Untimed 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

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
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

Clinical Features Cutaneous Lesion
- location → extremities, face, abdomen, & 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.
- It 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

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 → 31 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 → direct drug effect → not HAE.

Vasopressor in Local Anesthetics

- Epinephrine in local anesthesia:
  - Epinephrine can cause release of vasopressin.
  - Vasopressin activates Factor XII to Factor XIIa.
  - 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.
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 Clr, Cls, 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

Pathophysiology of HAE

- 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

Pathology 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

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

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

<table>
<thead>
<tr>
<th></th>
<th>C4 Level</th>
<th>C1-INH Level</th>
<th>C1-INH Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I HAE</td>
<td>Low</td>
<td>Low</td>
<td>Low &lt; 50% normal</td>
</tr>
<tr>
<td>Type II HAE</td>
<td>Low</td>
<td>Low or elevated</td>
<td>Low &lt; 50% normal</td>
</tr>
<tr>
<td>Type III HAE</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

- 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

Agents Used to Manage HAE

- C1 esterase
- 122
- DDAVP (1-deamino-8-D-arginine vasopressin)
- tranexamic acid
**C1-INH Replacement Therapy**

- plasma derived C1-INH concentrate (Berinert)
  - nanofiltered, bophilized, & 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

- 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
- 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

**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

**Current Short Term Prophylaxis**

- As of 2014
  - Do not rely on androgens, tranexamic acid, or 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
- $$$$$$$
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 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | No. of tooth    | No. of HAE      | Facial edema    | Laryngeal edema |
|                                | extraction      | attacks          | (visceral)      | (visceral)      |
| Prophylaxis with pdC1-INH      | 79              | 12              | 3               | 1               |
| Concentrate                    |                 |                 |                 |                 |
| Prophylaxis without pdC1-INH   | 92              | 4               | 1               | 1               |
|                                 |                 |                 |                 |                 |
|                                 | 12               | 4               | 4               | 3               |
| Without prophylaxis            | 377             | 136             | 86              | 28              |

- 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\(^4\)

- 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 preoperatively or 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

Where do you treat these patients

- Office → Outpatient Center → Inpatient
  - OMFS has all 3 available
  - What about the general dentist?
  - Is it safe to do these patients in the office with the newer agents?

- Discharge to home
  - Agents for use at home
  - Who is trained to use them
  - Doctor liability
  - Need discussion with patient, family, and allergist

- Treatment Plan
  - Sedation is advisable because you want as much dentistry in 1 appointment as possible due to costs of medications

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 (allergic vs non allergic reaction)
- 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
- angiotension 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

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

7/10/2018

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Curr Opin Anesthesiol. 2012:25:1
**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 Angiotensin II levels
  - 2 fold increase in Bradykinin levels
  - AT2 receptors are activated to increase kinin levels and stimulate B2 receptors

ARBs prevent angiotensin II vasoconstriction at AT1 receptors

ARBs do not block AT2 site

AT2 site leads to ↑ in bradykinin which increases the 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:
  - some of the reactions are indeed allergic in nature
  - epinephrine will work
  - if it is not a mast cell mediated response
  - agents will be ineffective
  - 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**

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

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

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**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 vitals and clinical presentation**

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**Proposed Guidelines for Use in HAE**

Confirmed or diagnosis of HAE

Based on extremity involvement of edema only

Laryngeal involvement

Supportive care and monitor closely for progression of angioedema, assess compromise

Airway compromise and endotracheal intubation as needed

Emergent intubation

**Icotinbant 30 mg subcutaneously**

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ACE-I is ACE inhibitor

ARB is angiotensin receptor blocker

FFP= fresh frozen plasma

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

Proposed Guidelines for ACE-Induced Angioedema

Thank you
Any Questions?

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