



# Perioperative Allergic Reactions

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## Key Concepts to Master

- Perioperative hypersensitivity reactions may be difficult to diagnose as symptoms may be masked by effects of surgery and anaesthesia.
- A good outcome in life-threatening anaphylactic reactions depends on timely diagnosis and appropriate treatment with epinephrine and fluid replacement.
- Patients should be referred for subsequent allergy investigation and the anaesthetist should provide detailed information about all drugs and substances used perioperatively.

Curr Opin Anaesthesiol.2020;33:448

## 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 → slow PO absorption
- IgE antibody mediated
- mast cell & basophil release of vasoactive mediators
  - histamine, prostaglandins, & leukotrienes

## Clinical Signs of Reaction

- clinical signs
  - urticaria & pruritus
  - angioedema → not just lips, tongue, & larynx
  - anaphylaxis
- antigens
  - food
  - insect stings & venom
  - medications
  - occupational allergens

## Immediate Allergic Reactions

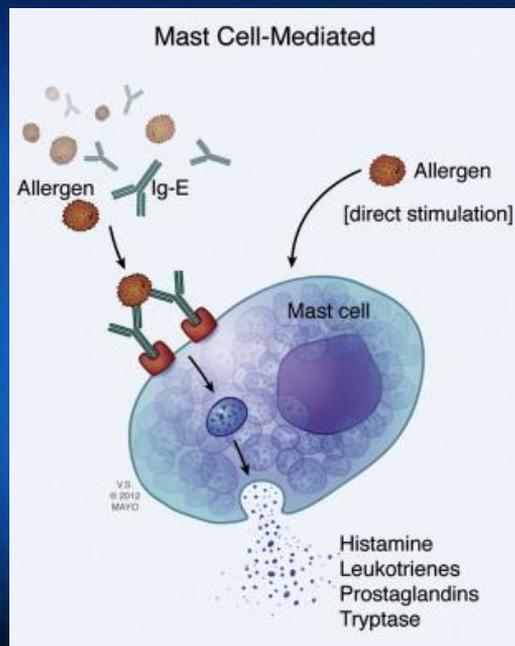
## Urticaria ( Hives )

- 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



## 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
  - 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**



J Clin Anesth. 2013;25:335-343

**Ab binds to mast cell**

**Antigen cross links 2 Ab**

**Release mediators**

**Some mediators can be measured in laboratory to diagnose IgE reaction**

## Urticaria 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 )
- Urticaria can persist for > 24 hours → continue with diphenhydramine for itching → 25 to 50 mg Q6h → sedation precautions

## Management: Antihistamines

- H<sub>2</sub> antihistamine → famotidine ( Pepcid )
  - see more improvement in urticaria size & resolution
  - **less improvement in pruritis**
  - dose in adults: 20 mg IV or 20 mg PO
  - dose in children: 0.25 mg/kg IV over 2 minutes
- Unlikely to keep in office
- Not commonly used → reserved for moderate to severe allergic reaction
- Ranitidine → no longer used → cancer risk

## Angioedema

- Transient swelling of **deep dermis, subcutaneous, or submucosal tissues**
- **Non pitting edema** → **any body location**
  - head, neck, lips, tongue, mouth, pharynx, or larynx
  - isolated area or spread to all of these sites
- Non pruritic → unlike urticaria

# Angioedema

- 2 Mediators for angioedema

## IgE Mediated Reaction

### → Histamine Allergic Reaction

- swelling occurs in minutes
- resolves < 24 hours

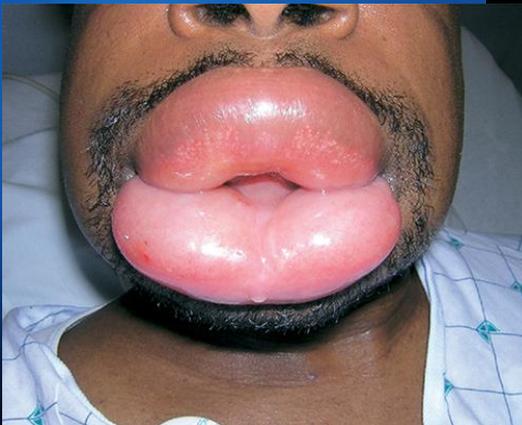
## Bradykinin reaction

### → non allergic reaction

- swelling onset in hours
- resolves > 24 hours

## Angioedema

Lips



Periorbital

## Urticaria vs Angioedema

- urticaria is not life threatening
  - angioedema involving the airway is life threatening
- urticaria + angioedema at same time → more severe rxn
  - ↑ 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% cases	→	urticaria + angioedema
40% cases	→	isolated urticaria
10% cases	→	isolated angioedema

## Management of Angioedema

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

## Anaphylaxis → General Concepts

- 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
  
- Anaphylactoid or **Non - immune anaphylaxis**
  - non -immune direct release of mediators from mast cells & basophils
  - activation of classical complement pathway
  - activation of kallikrein – kinin pathway
  - bradykinin mediated vasodilation & edema
  - treated just like allergic anaphylaxis → at onset of reaction

## 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 1<sup>st</sup> reaction
  
- Protracted anaphylaxis
  - lasts for hours or days ( weeks )
  - rare reaction

## Frequently Seen 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 → Tongue & Larynx**  
**ONLY 20% INCIDENCE**

**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
  - see

↓ coronary blood flow    ↓ myocardial contractility  
 ↑ dysrhythmias            ↑ risk of cardiac arrest

Curr Opin Allergy Clin Immunol. 2014; 14: 309

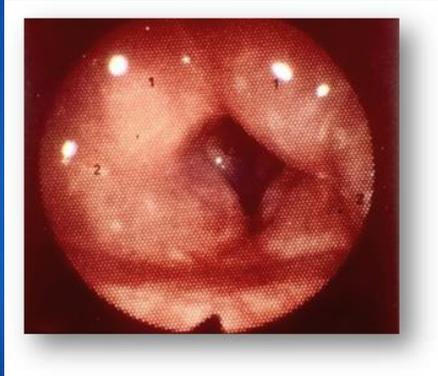
**Table 1**  
Clinical diagnosis of anaphylaxis

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

# Anaphylaxis



Laryngeal edema courtesy of Dr. Bosack



Other signs: angioedema & urticaria

# Perioperative Anaphylaxis

## When to Suspect Perioperative Anaphylaxis

- Unexplained Hypotension
- Unexplained Bronchospasm
- Unexplained Tachycardia → even Bradycardia
- New onset Angioedema
- Cutaneous Flushing associated with 1 or more of above
- Sudden Cardiac Arrest
- Old anesthesia tenet → after injection of medication → sudden onset of tachycardia & hypotension = anaphylaxis until proven otherwise

Anesth Intensive Care Med.2019;20:702

## Grading Perioperative Anaphylaxis

Grade	Definition	Signs
I	<b>Mild Reaction: Cutaneous &amp; Mucosal Signs</b>	Generalized urticaria, rash, erythema, ± angioedema
II	<b>Moderate Reaction Single or Multiple Organs</b>	<b>Mucocutaneous Signs:</b> ± Grade I signs <b>CVS:</b> Moderate Hypotension & Tachycardia, may see onset of Bradycardia <b>Respiratory:</b> Moderate wheeze & dyspnea <b>GI:</b> N/V, diarrhea, & abdominal pain
III	<b>Life-threatening Anaphylaxis Multiorgan</b>	<b>Severe</b> → Hypotension, Tachycardia or Bradycardia, Bronchospasm, Dysrhythmias, & GI signs <b>Mucocutaneous Signs:</b> ± Grade I signs
IV	<b>Cardiac Arrest</b>	PEA & No cutaneous signs

J Allergy Clin Immunol Pract.2019;7:2134

Curr Opin Anesthesiol.2020;33:448

## Grading Perioperative Anaphylaxis

- Perioperative urticaria & rash → not the 80% incidence seen in other types of anaphylaxis
  - hidden from view by drapes
  - may not be seen until perfusion and BP restored
- Grade I & II cases → not life threatening
- Grades III & IV → life threatening
- Grade V → Death

## Perioperative Anaphylaxis

- Perioperative incidence → 1: 10,000
  - some reports → 1:7000    others as low as → 1:20,000
  - risk for practitioner seems low → 1 case every 7 years
- Perioperative anaphylaxis
  - IgE anaphylaxis                      60% cases
  - Anaphylactoid                        10.6% cases
  - fatal in 3 to 9% of cases
  - occurs within minutes → even 1 minute after IV dose of drug

Anesth Analg. 2008;107:620    AANA J.2012;80:129    J Allergy Clin Immunol Pract.2019;7:2134  
 Br J Anesth.2019;123:e50                      UptoDate.accessed 2021

## Perioperative Anaphylaxis

- Awake patients → can report early signs of anaphylaxis
  - malaise, pruritus, dizziness, wheeze, & dyspnea
- Anesthesia cases → can have delay in diagnosis
  - patient can not report symptoms → deep sedation or GA
  - TIVA agents → cause hypotension → possible to see tachycardia
  - Inhalation agents → hypotension & tachycardia
  - Airway manipulation → possible bronchospasm
  - Anaphylaxis = all of above

Curr Opin Anesthesiol. 2020:

## Perioperative Anaphylaxis

- Common Signs
  - Hypotension
  - Tachycardia more frequent than bradycardia
  - Bronchospasm → more common in patients with underlying airway hyperactivity ( asthma, COPD, and obesity )
  - Ventilating patient → ↑ resistance to bag ventilation
  - SpO2 desaturations & ↓ end tidal CO2

Anesthesia Intensive Care Med.2019

# Perioperative Anaphylaxis

Hypotension	100% cases
Non urticarial Rash	60%
Tachycardia	50%
Bronchospasm	50%
High Airway Pressures	50%
Low Saturations	40%
Low Capnography	30%

Females 3X > Males

Allergic Agent Determines  
When Reaction Occurs

- Induction
- Intraoperative
- Emergence

# Perioperative Anaphylaxis vs Other Settings

Manifestations of anaphylaxis	In other settings	In perioperative settings
Upper respiratory tract/laryngeal edema	Throat tightness, change in voice quality	Difficulty with intubation
Lower respiratory tract/bronchospasm	Shortness of breath, wheezing, repetitive cough	Increase in ventilatory pressure needed to inflate lungs
		Increase in end-tidal CO <sub>2</sub>
		Decrease in arterial oxygen saturation
Cardiovascular system/hypotension	Dizziness, tunnel vision Collapse without warning signs uncommon	Cardiovascular collapse common (first detected manifestation in one-half of cases)  Arrhythmias and cardiac arrest are more common
Skin	Flushing, itching, or urticaria (present in >90% of cases)	Cutaneous signs and symptoms may be absent or present but hidden by surgical drapes
		Patient cannot report itching

UpToDate 2021

# Agents Causing Perioperative Anaphylaxis

2003 to 2015

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

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

# Agents Causing Perioperative Anaphylaxis

2016 to 2020

<b>Antibiotics</b>	<b>47 to 55%</b>
<b>NMB Agents</b>	<b>33%</b>
<b>Chlorhexidine</b>	<b>9%</b>
<b>Patient Blue Dyes</b>	<b>5%</b>
<b>Latex</b>	<b>Low risk</b>
<b>Anesthetic Agents</b>	<b>Low risk</b>

J Allergy Clin Immunol Pract 2019 Br J Anesth. 2019 Curr Opin Anesth 2020

## Anesthetic Agents: Antibiotics

- In US → replaced NMB agents as # 1 medication risk for anaphylaxis
- Beta Lactam Agents
  - Penicillins & Cephalosporins
  - Cefazolin ( Ancef ) → #1 agent
- Vancomycin & Quinolones are next

Onset Time Reaction	Percentage of Cases
Within 5 mins	74%
6 to 10 mins	18%
11 to 15 mins	5%

J All Clin Imm.2019

## Anesthetic Agents: Antibiotics

- Antibiotic Test Dose
  - attempt to see if patient is allergic → trying to decrease severity of anaphylactic reaction
  - result → caused 20% of the reported anaphylactic reactions
  - anaphylaxis is not dose dependent
  - test dose is not advised
- IV antibiotics in the office
  - infuse the agent before the anesthetic
  - patient is awake & able to describe the reaction

Anesthesia & Intensive Care Med.2019;20:12

## Anesthetic Agents: NMB Agents

- Were the most common trigger → replaced by antibiotics
- Triggers during 1<sup>st</sup> 30 minutes of case → induction or after
- Women 3X more frequent than men
- IgE immediate anaphylactic reaction → majority of cases
- Non IgE through direct mast cell activation → minor component
- 15 to 50% of NMBA anaphylaxis cases → no previous exposure to NMB
  - tertiary & quaternary ammonium cpds in OTC cosmetics are the risk

Anesthesiology.2015;122(1) AANA J.2012;80:129 J All Clin Immun Pract.2019

## Anesthetic Agents: NMB Agents

- Succinylcholine → 2 X risk of non – depolarizing agents
- NMB agents Anaphylaxis Risk
  - succinylcholine > rocuronium → most likely allergic risk
  - atracurium > cisatracurium → low allergic risk
  - Succinylcholine accounts for up to 60% of anaphylactic cases
- Cross sensitivity among agents
  - 60 to 70% incidence → 7% risk of cross sensitivity to all NMB agents
  - variable patterns

## Sugammadex

- Reversal agent for non depolarizing agents → commonly rocuronium
- Reports → sugammadex allergic reactions
- Onset → at end of case to reverse NMB agent
- Possible allergic reaction to sugammadex – rocuronium complex
- Case report → sugammadex used to try and reverse rocuronium anaphylactic reaction → no evidence it worked

J Allerg Clin Immunol Pract.2019

## Latex

- IgE – Ab immediate reaction to protein in natural rubber
- Onset → 30 + minutes after exposure → rarely seen on induction
- Historically → 2<sup>nd</sup> or 3<sup>rd</sup> leading cause of anaphylaxis
- Currently on decrease
  - products now are highly refined but use is on decrease → non latex products used
  - 2005 → incidence was 18%
  - 2012 → incidence was 5%

## Disinfectants & Anaphylaxis

- Chlorhexidine → IgE immediate allergic reaction
  - reactions → urticaria to anaphylaxis
  - used in urology for disinfection of catheters
  - also cause skin reactions
  - onset → 20 to 40 minutes into case
  - no reports for oral rinse
  
- Povidone-Iodine ( Betadine )
  - anaphylaxis is rare
  - more contact dermatitis ( Type IV cell mediated reaction )
  - can be used if have shellfish allergy

## Anesthetic Agents

- Methohexital
  - IgE immediate reaction
  - Women > Men
  - Replaced by propofol
  
- Propofol
  - allergic reactions to isopropyl groups or phenol ring in drug
  - egg issue → egg allergy is egg white → propofol has lecithin from egg yolk
  - no reports of reaction to propofol in egg , soy, or peanut allergic patients even if the allergy was anaphylaxis
  - safe to use

J Allergy Clin Immunol Pract.2019;7:2134

## 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 → allergy in 1:100,000 to 1:200,000 cases
  - 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: **mepiridine**, 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
  - *no cross - reactivity* → between the 3 subgroups
  - *+ cross - reactivity* → between morphine & codeine
  - *no cross - reactivity* → between the phenylpiperidines

**Allergic to Fentanyl  
Remifentanyl is OK**

Anaesth Intensive Care.2012; 40: 216

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

## Option A Opioid Drug Options

- **Option A** : may be pseudoallergy from histamine
  - nonopioid analgesic: tylenol or NSAID
  - avoid codeine, morphine, and meperidine → histamine release
    - 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

[www.prescriberletter.com](http://www.prescriberletter.com) accessed 5/2015

## More Severe Reaction

<b>Severe hypotension</b>	<b>Go to B</b>
<b>Skin reaction other than hives ( generalized rash )</b>	<b>Go to B</b>
<b>Breathing, speaking, or swallowing difficulties</b>	<b>Go to B</b>
<b>Angioedema</b>	<b>Go to B</b>

## Option B Opioid Drug Options

- Option B: may be true allergy
  - non opioid: NSAID or Tylenol
  - use 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](http://www.prescriberletter.com) accessed 5/2015

## 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
  - ↑ vasoconstriction & peripheral vascular resistance
  - ↓ mucosal edema in airway
- $\beta_1$  adrenergic agonist
  - ↑ inotrope & chronotrope
- $\beta_2$  adrenergic agonist
  - ↑ bronchodilation
  - ↓ mediator release from mast cells & basophils

UpToDate. accessed 2021

## History of Epinephrine Use

- 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 3<sup>rd</sup>
  - 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 Epinephrine for Perioperative Allergic Rxns

- Current data → IV dosing based upon Reaction Grade

	IV Epinephrine	IV Fluids Saline
<b>Grade II</b>	<b>10 to 20 mcg IV Bolus</b>	<b>500 ml rapid bolus</b>
<b>Moderate Allergic Reaction</b>	<b>Inadequate response after 2 minutes</b>	<b>Review response</b>
	<b>Escalate to 50 mcg IV</b>	<b>Repeat as needed</b>
	<b>Repeat every 2 minutes</b>	
	<b>No IV → 300 mcg IM</b>	

## IV Epinephrine for Perioperative Allergic Rxns

	IV Epinephrine	IV Fluids
Grade III	50 mcg IV	1 Liter Rapid Bolus
Severe Allergic Reaction	No Response after 50 100 mcg IV	Review Response
	Inadequate After 2 mins Escalate to 200 mcg	Repeat as needed Up to 30 ml/kg
	Repeat Q 2 minutes	

**Severe Rxn: 50 mcg IV → 1 min then 100 mcg → 200 mcg Q 2 min prn**

Br J Anesth. 2019 Curr Opin Anesth.2020

## IV Epinephrine for Perioperative Allergic Rxns

- Grade IV Anaphylaxis
- Most likely in PEA rhythm
- IV Epinephrine → 1 mg IV → Repeat as per ACLS
- Chest Compressions if no pulse
- Chest Compressions with pulse
  - SBP < 50
  - End tidal CO<sub>2</sub> < 20

## 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 = 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

**BEST WAY**

## Vasopressin for Refractory Hypotension

- Patients on beta blockers, ACE-I, and ARBs can be resistant to the vasopressors
- Develop refractory hypotension & bradycardia
- Exogenous Vasopressin can treat this hypotension
- Vasoconstriction by stimulating V<sub>1</sub> receptors in vessels
- Onset → almost immediate
- Peaks → 30 to 60 minutes
- Duration of pressor effects → 30 to 60 minutes

AANA J.2013;81:133

## Vasopressin

- Metabolism in liver & by kidney vasopressinases
- Side effects
  - increased SVR can decrease perfusion to kidneys, liver, and mesentery
  - vasoconstriction in coronary vessels
  - myocardial ischemia & arrest at high doses
- antidiuretic effects can last 2 to 8 hours → water intoxication possible so water restriction considerations

## Vasopressin

- Ampule = 20 U/ml
- Dilute to 1 U/ml
- Initial bolus → 0.5 to 1.0 units
- Infusion → 0.01 to 0.5 U/min adjusted to clinical response
- Case report 2008 refractory hypotension resistant to phenylephrine, ephedrine, and Epi
  - 0.4 U bolus repeated; 2 U Q 10 min then infusion 0.04 U/min over 90 minutes
- Cost: 20U = \$ 253.00 checked 1/21

Anest Analg. 2008;107:620-4

J Clin Anesth.2008;20:135

## Vasopressin & Glucagon in Anaphylaxis

- Hypotension Refractory to Epinephrine
- Vasopressin bolus → 1 to 2 Units IV Bolus
- Glucagon bolus → 1 to 5 mg IV over 5 minutes  
→ 1 to 2 mg IV over 2 minutes

Cost: Glucagon \$244.00 for 1 mg/ml 1/21

UpToDate 2021 Br J Anesth 2019

## Refractory Hypotension

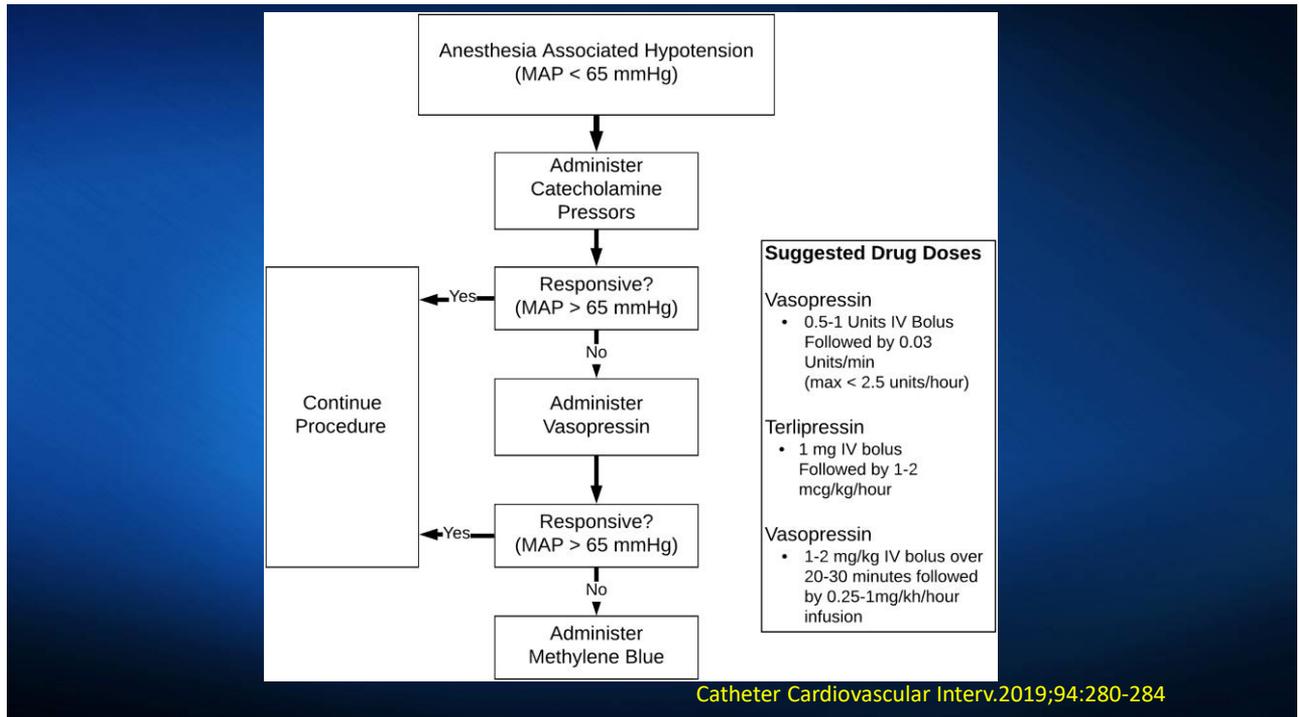
- Glucagon
  - acts independent of the beta- adrenergic system
    - get ↑ in cyclic AMP → increases muscle contractions
  - ↑ inotropic & chronotropic effects of heart
  - initial dose = 1 to 5 mg then start infusion
    - infusion 1 to 2.5 mg/hr.
  - rapid bolus = N/V
  - Expensive

# Glucagon



# Methylene Blue

- Nitric oxide (NO) causes vasodilation
- Methylene Blue binds to NO synthase to decrease NO production & increase vascular tone
- Dose → 1 to 2 mg/kg bolus over 20 to 30 minutes
  - follow with infusion → 0.25 to 1 mg/kg/hr titrated to MAP
- Side effects
  - hemolytic anemia in G6PD deficiency
  - dysrhythmias, green-blue skin color & urine, decreased renal blood flow



## 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 1<sup>st</sup> 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

# 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 → 2.5 mg in 2.5 ml saline
- MDI inhaler → 4 to 8 puffs





# KAB Absorber





## Glucocorticoids

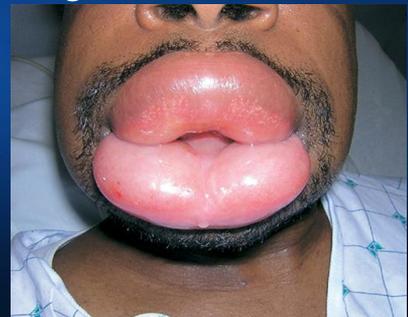
- will **not relieve initial** symptoms in anaphylaxis
  - take several hours to reach an effect
- may **prevent biphasic or protracted anaphylaxis**
  - **no proof** just a preventive measure
- **hydrocortisone will have fastest onset**
- Adult dose
  - hydrocortisone 1 to 2.5 mg/kg IV ( 250 mg IV )
  - 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

## 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

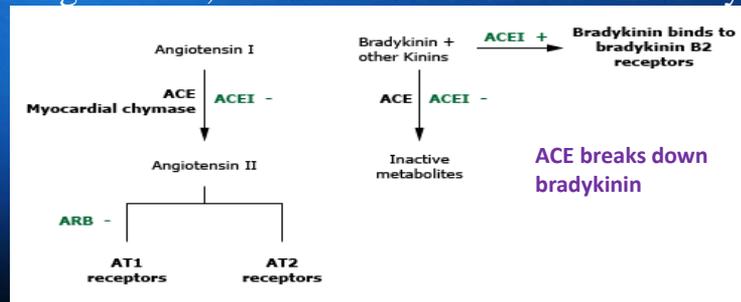
- most cases present as **swelling of lips, tongue, or face**
- occasional episodes of intestinal swelling
  
- may involve **pharynx & larynx**
  - 10% incidence of UAO
- **will not see pruritus or urticaria**

## Clinical Features

- **swelling** develops in **minutes to hours**
- resolves in 24 to 72 hours ( allergic vs non allergic reaction )
- **50%** cases occur during the **1<sup>st</sup> week** of drug use
- **66%** occur **within 3 months**
  
- sometimes it will take years before you see angioedema

# Angiotensin Converting Enzyme

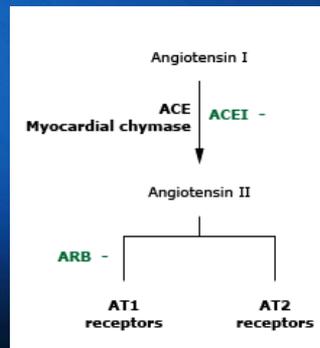
- converts angiotensin I to angiotension II
  - angiotensin II causes vasoconstriction
- ACE is also a kininase enzyme
  - prevents bradykinin formation
  - in ACE-I angioedema, can see a 10 fold increase in bradykinin levels



# 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

ARBs prevent angiotensin II vasoconstriction at AT1 receptors



ARBs do not block AT2 site

AT2 site leads to ↑ in bradykinin which increases the angioedema

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
  - some of the reactions are indeed allergic in nature
    - epinephrine will work if it is an allergic reaction
  - 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

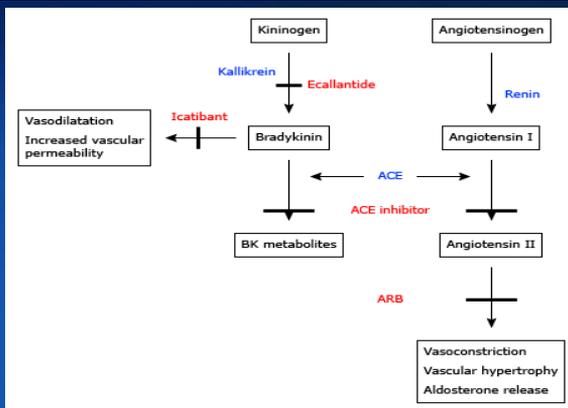
## Renin – Angiotensin – Aldosterone - System (RAAS) Inhibitor Induced Angioedema

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

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# 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**



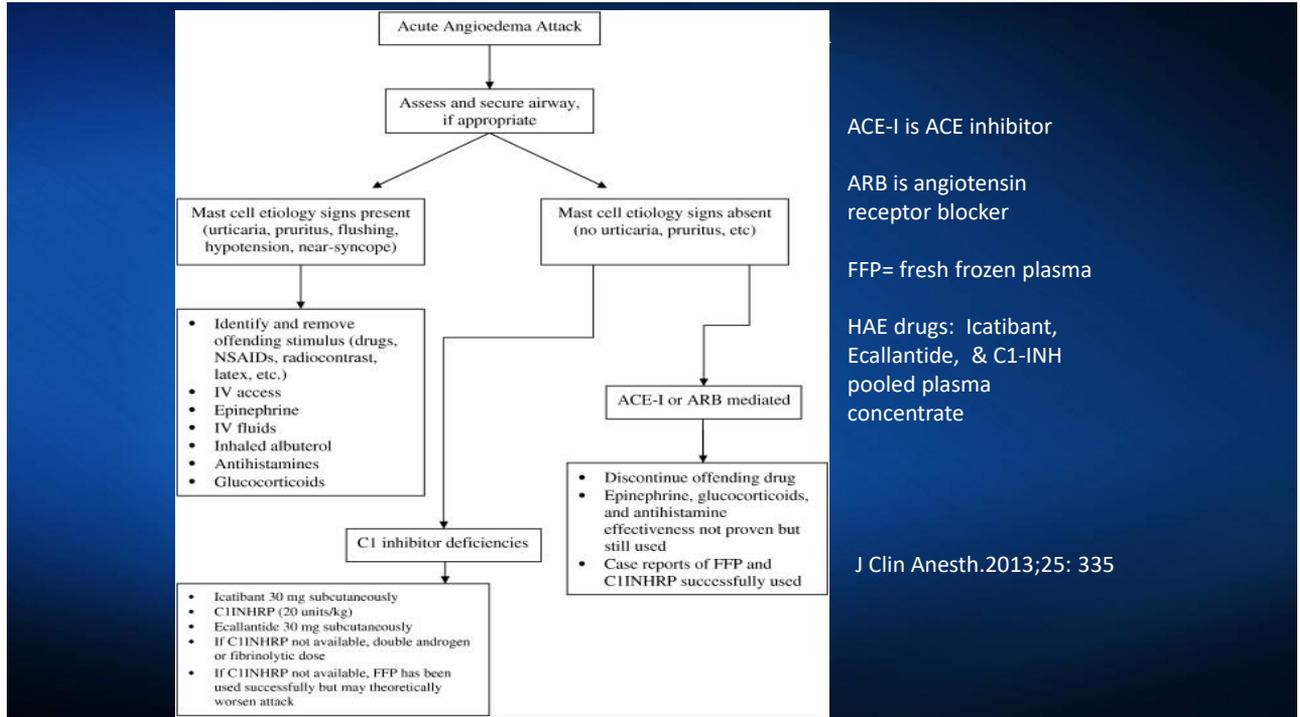
Blue = enzymes  
Red = drugs

## 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



# Thank you



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