Anaphylaxis: Recognition and Management

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Disclosure

• Teva Respiratory: Honoraria | Speaker / Advisory Board
• Sunovion: Honoraria | Speaker / Advisory Board
• GlaxoSmithKline: Dividends | Stockholder
• Johnson & Johnson: Dividends | Stockholder
Lecture objectives:

• By the end of this lecture, the participant should be able to:
  – Understand anaphylactic reaction pathophysiology
  – Identify symptoms of anaphylaxis
  – Describe the basic anaphylaxis treatment protocol
  – Discuss treatment of refractory anaphylaxis
  – Describe basic precautions to prevent anaphylaxis
Key Points

- Anaphylaxis: an acute, life-threatening systemic reaction with that results from the sudden systemic release of mediators from mast cells and basophils
- Varied mechanisms, presentations, and severity
- Almost always unanticipated
- Mild may rapidly progress to severe
- More rapid onset symptoms = more dangerous event
- Delay in treatment can be fatal due to airway obstruction or vascular collapse
Key Points

✓ Incidence of systemic reactions to immunotherapy injections is about 0.5% (1 in 200)

✓ Incidence of fatal anaphylaxis to immunotherapy injections is approximately .00004% (1 in 2.5 million)

✓ Although uncommon, physicians and patients must be prepared for immunotherapy systemic reactions

✓ Every facility must have a plan for anaphylaxis

✓ Physicians and office staff should maintain clinical proficiency in anaphylaxis management
Mechanism of anaphylaxis

- Results from the sudden systemic release of mediators from mast cells and basophils
- Increased vascular permeability with extravascular space transfer is characteristic
- Usually but not always immunologic
  - (Anaphylactoid reactions are IgE independent)
Beware of Statistics

The Mexican government had a highway problem: The Viaducto, new 4 lane highway, overcrowded shortly after it was completed.

No money left for additional construction.

Decided to repaint the highway stripes to make a 6 lane highway.

Government celebrated that highway capacity was increased 50% (4 lanes + 2 = 50% increase)
Unintended consequences

• Soon after highway reopened with new lines, marked increase in traffic accidents noted.

• After deliberation, government decided to repaint highway for 4 lanes.

• Reduced highway capacity by 33% (removing 2 lanes from 6 is 33% reduction)
The government proudly noted that despite setbacks their efforts increased highway capacity on the Viaducto by 17%

(50% increase minus 33% reduction=17%)
Terminology

• Anaphylaxis – IgE-mediated reaction
• Anaphylactoid – same clinical picture but is not IgE mediated.
• Anaphylactic – description of the condition; can be caused by IgE or non-IgE-mediated reaction
Anaphylaxis

• Coined by Portier and Richet in 1902
• Attempted to immunize dogs to sea anemone venom
• Dogs reacted fatally to previous nonlethal dose
• Phenomenon was opposite of prophylaxis, hence anaphylaxis
Anaphylaxis during Immunotherapy: Risk Factors

- Buildup immunotherapy: 90%
- Active asthma: 46%
- New vial, 1st inject (non-error): 10%
- Prior systemic reaction: 7%
- Vial prepared in another office: 6%
- Error (wrong patient's vial): 3%

Hurst DS, et al. Oto-HNS 1999;121:553-561
Fatal Anaphylaxis during Immunotherapy: RF

- Labile or symptomatic asthma
- Dose increase phase of IT
- High sensitivity by testing
- Previous SR/Anaphylaxis with prior injections
- Active allergen season
- New vial
- Human error (dosage, administration, treatment, equipment, observation)

Clinical presentation

**Urticaria and angioedema:** most common manifestations but can be delayed or absent in rapidly progressive anaphylaxis

**Loss of airway and cardiovascular collapse** are the most frequent cause of fatalities

The more rapidly anaphylaxis occurs after injection, the more likely it is to be severe and potentially life-threatening
Cutaneous and Respiratory signs are most common in Anaphylaxis

<table>
<thead>
<tr>
<th>Area</th>
<th>Percentage</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td>&gt;90%</td>
<td>Urticaria, Angioedema, Flushing, Itching without rash</td>
</tr>
<tr>
<td>Respiratory</td>
<td>60%</td>
<td>Dyspnea, wheeze, Upper airway angioedema, Rhinitis</td>
</tr>
<tr>
<td>Abdominal</td>
<td>30%</td>
<td>Nausea, vomiting, Abdominal cramps, diarrhea</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>30%</td>
<td>Tachycardia, hypotension → dizziness, syncope</td>
</tr>
<tr>
<td>Other</td>
<td>1-8%</td>
<td>Headache, substernal pain, seizure</td>
</tr>
</tbody>
</table>

Symptoms and signs:

- The skin - diffuse or localized erythema, pruritus, urticaria, and/or angioedema
- Upper and lower airways - dysphonia, stridor, cough, wheezing, or shortness of breath
- Tachycardia is the ‘rule’, but it can be absent
- Cardiovascular system - hypotension with or without syncope and/or cardiac arrhythmias
- Level of consciousness - impairment might reflect hypoxia
- GI - nausea, vomiting, or diarrhea
Anaphylaxis can develop rapidly and is unpredictable

- Up to 50% of intravascular fluid can transfer into the extravascular space within 10 min!
- As a result, hemodynamic collapse might occur rapidly with little or no cutaneous or respiratory manifestations
- Not immediately life threatening, but can progress rapidly unless treated promptly
Anaphylaxis can be delayed or biphasic

- Most systemic reactions occur within 20 or 30 minutes after allergen vaccine administration
- Some reactions might develop later
- Late-phase or biphasic reactions can occur 8 to 12 hours after the initial attack
- Protracted and severe anaphylaxis might last up to 32 hours, despite aggressive treatment
Classification of Anaphylaxis Severity

• Ring and Messner
  – Grade I: cutaneous manifestations
  – Grade II: mild respiratory and CV effects
  – Grade III: severe multisystem involvement
  – Grade IV: respiratory and cardiac arrest

• Brown
  – **Mild**: generalized erythema, urticaria, periorbital edema, angioedema
  – **Moderate**: dyspnea, stridor, wheeze, N/V, dizziness, diaphoresis, chest or throat tightness, abdominal pain
  – **Severe**: hypoxia, hypotension, neurologic compromise, cyanosis, confusion, collapse, LOC, incontinence

Brown SGA. *JACI* 2004;114:371-6
Conditions that “contain” some single anaphylactic signs but are not necessarily anaphylaxis:

- Asthma
- Urticaria
- Urticaria-angioedema
- Angioedema
Other diagnoses that can cause dramatic patient collapse:

- Vasodepressor (vasovagal) reactions
- Acute anxiety (panic attack or hyperventilation)
- Myocardial dysfunction
- Pulmonary embolism
- Systemic mast cell disorders
- Foreign-body aspiration
- Acute poisoning
- Hypoglycemia
- Seizure disorder
Anaphylactoid Reaction

- Non-IgE mediated immune reaction with generalized mast cell degranulation, complement activation
- Can happen on first exposure to a foreign substance
- Clinically similar to Anaphylaxis
- Causes: exercise, drugs (NSAIDs), radiodensity agents
Vasodepressor (vasovagal) reaction

- Most common condition confused with anaphylaxis
- But it should NOT: it is VERY DIFFERENT
- Urticaria is ABSENT
- The skin is typically cool and pale
- The heart rate is typically BRADYCARDIC
- Rarely have Bronchospasm or Dyspnea
- The blood pressure is usually normal or increased (after patient collapses)
## Anaphylaxis vs. Vasovagal

<table>
<thead>
<tr>
<th>Anaphylaxis</th>
<th>Vasovagal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse rapid</td>
<td>Pulse slow</td>
</tr>
<tr>
<td>Blood pressure ↓</td>
<td>Blood pressure nl</td>
</tr>
<tr>
<td>Skin red/warm</td>
<td>Sweating/pallor</td>
</tr>
<tr>
<td>Cough / wheezing</td>
<td>No cough or wheeze</td>
</tr>
<tr>
<td>Itching/urticaria</td>
<td>No itching/urticaria</td>
</tr>
<tr>
<td>Feeling of doom</td>
<td>No feeling of doom</td>
</tr>
</tbody>
</table>

Add reference here
Key Treatment Points

- Epinephrine, oxygen, and volume replacement are the most important therapeutic agents.

- Fatalities during anaphylaxis usually result from *delayed administration of epinephrine* and from severe respiratory complications, cardiovascular complications, or both.

- There is no absolute contraindication to epinephrine administration in anaphylaxis.
Table 77-2  Frequency of Occurrence of Signs and Symptoms of Anaphylaxis

<table>
<thead>
<tr>
<th>SIGNS/SYMPOMS</th>
<th>PERCENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria and angioedema</td>
<td>88</td>
</tr>
<tr>
<td>Dyspnea, wheeze</td>
<td>47</td>
</tr>
<tr>
<td>Dizziness, syncope, hypotension</td>
<td>33</td>
</tr>
<tr>
<td>Nausea, vomiting, diarrhea, cramping abdominal pain</td>
<td>30</td>
</tr>
<tr>
<td>Flush</td>
<td>46</td>
</tr>
<tr>
<td>Upper airway edema</td>
<td>56</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>16</td>
</tr>
<tr>
<td>Substernal pain</td>
<td>6</td>
</tr>
<tr>
<td>Itch without rash</td>
<td>4.5</td>
</tr>
<tr>
<td>Seizure</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Immediate and initial intervention: ABCs/Epi/Oxygen/Fluids

(1) Assessment and maintenance of airway, breathing, circulation and level of consciousness (adequacy of mentation) are necessary before proceeding to other steps.

(2) Epinephrine administration and the maintenance of adequate oxygenation and intravascular volume have high priority.

*IF THERE IS ANY DOUBT, IT IS BETTER TO ADMINISTER EPINEPHRINE*
When in doubt, administer Epinephrine

- Use aqueous epinephrine 1:1000 dilution (1 mg/mL)
- For adults, inject IM or SQ: 0.2 to 0.5 mL
- For children, inject IM or SQ: 0.01 mg/kg, maximum 0.3-mg dosage
- May re-inject every 5 minutes, as necessary, to control symptoms and increase blood pressure
- Consider dose-response effects
- If appropriate, the 5-minute interval can be liberalized to permit more frequent injections
Subsequent emergency care that might be necessary depending on response to Epinephrine:

1. Place patient recumbent and elevate lower extremities
2. Establish and maintain airway
3. Administer oxygen
4a. Consider NSS IV for fluid replacement and venous access
4b. Consider IV epi
5. Consider diphenhydramine
6. Consider ranitidine/cimetidine
7. Consider inhaled b-agonist
8. Consider vasopressor IV
9. Consider glucagon infusion
10. Consider systemic glucocorticosteroids
11. Prepare for transportation to emergency department
Place patient in the recumbent position and elevate the lower extremities, as tolerated symptomatically.
Establish and maintain airway

Consider ventilatory assistance with facemask and ambu-bag

Consider endotracheal intubation or cricothyroidotony
Administer oxygen

• Indicated in patients with:
  – Prolonged reactions
  – Multiple doses of epinephrine
  – Pre-existing hypoxemia
    Myocardial dysfunction
  – Receive inhaled β-agonists as part of therapy for anaphylaxis

• Pulse oximetry and/or ABG (where available) should guide oxygen therapy
Consider a normal saline intravenous line for fluid replacement and venous access

Increased vascular permeability may move 50% of the intravascular fluid into the extravascular space within 10 minutes

1 to 2 L of normal saline → rate of 5 to 10 mL/kg in the first 5 minutes, followed by slower infusion

Crystalloid volumes (eg, saline) of up to 7 L might be necessary

Children should receive up to 30 mL/kg in the first hour
IV administration of epinephrine

- Epinephrine administered IV CAN LEAD TO POTENTIALLY LETHAL ARRHYTHMIAS

- Therefore use ONLY if there is
  - Cardiac arrest or profound hypotension and…
  - Failure to respond to intravenous volume replacement and…
  - Several injected doses of epinephrine have been administered
IV administration of epinephrine

- At the very least, try to monitor
  - Blood pressure every minute
  - Pulse measurements
  - Electrocardiographic activity

- If available, use continuous hemodynamic monitoring (eg, emergency department or intensive care facility)

- But…use of intravenous epinephrine SHOULD NOT BE PRECLUDED IN A SCENARIO IN WHICH SUCH MONITORING IS UNAVAILABLE if the clinician deems administration is essential after failure of several epinephrine injections
IV DOSING of epinephrine (ADULTS)

- Aqueous epinephrine 1:1000, 0.1 to 0.3 mL in 10 mL of normal saline
- Administer IV over several minutes and repeat as necessary
- Alternatively, add 1 mg (1 mL) of a 1:1000 dilution of epinephrine to 250 mL of D5W to yield a concentration of 4 mg/mL
  - Infuse at a rate of 1 to 4 μg/min (15 to 60 drops per minute with a microdrop apparatus [60 drops per minute = 1 mL = 60 mL/h]), increasing to a maximum of 10 μg/min
IV DOSING of epinephrine In CHILDREN

- Use a dosage of 0.01 mg/kg (0.1 mL/kg of a 1:10,000 solution; maximum dose, 0.3 mg)

- Alternative pediatric dosage by the "rule of 6" is as follows:

  
  \[
  0.6 \times \text{body weight (in kilograms)} = \text{the number of milligrams diluted to a total of 100 mL of saline; then 1 mL/h delivers 0.1 } \mu\text{g/kg/min.}
  \]
Consider H1 and H2 antihistamines

- Antihistamines are considered *second line therapy* to epinephrine
- Have a much slower onset of action than epinephrine
- *Should never be used alone in treating anaphylaxis*
- A combination of diphenhydramine and ranitidine is superior to diphenhydramine alone
Diphenhydramine (H1), ranitidine (H2) or cimetidine (H2) DOSING

- Diphenhydramine, 1 to 2 mg/kg or 25 to 50 mg per dose (parenterally)

- Ranitidine - 50 mg in adults and 12.5 to 50 mg (1 mg/kg) in children, can dilute in 5% dextrose to a total volume of 20 mL and injected intravenously over 5 minutes.

- Cimetidine - (4 mg/kg) can be administered intravenously to adults, but no pediatric dosage in anaphylaxis has been established
Bronchospasm

• Should respond to epinephrine, but…

• If resistant after adequate epinephrine:
  – Consider inhaled β-agonist (eg, nebulized albuterol, 2.5 to 5 mg in 3 mL of saline and repeat as necessary)
Hypotension refractory to epinephrine and volume

• Should respond to epi and volume, but…

• If refractory to volume replacement and epinephrine injections:
  – Consider vasopressor infusion
  – For example, dopamine (400 mg in 500 mL of 5% dextrose) can be infused at 2 to 20 μg/kg/min, titrated to maintain systolic blood pressure of greater than 90 mm Hg
  – Need continuous hemodynamic monitoring
Beta-adrenergic blockade

- Beta-adrenergic antagonists may cause more severe anaphylactic reactions
- Characterized by *paradoxic bradycardia*, profound hypotension, and severe bronchospasm
- *Epinephrine might not be effective*
Clinicians should *avoid* (where possible) administering beta blockers to patients who might or will be exposed to an anaphylactogenic stimulus:

- Allergen immunotherapy
- Immediate hypersensitivity skin testing
- Radiographic contrast media
- Hymenoptera venom anaphylaxis potential

Cardioselective or ophthalmic beta-blockers are not excluded
β blockers and anaphylaxis

“Allergy skin testing or immunotherapy is inadvisable in patients who take a β blocker orally or in the form of ophthalmic eyedrops”

Toogood JH. CMAJ 1987;136:929-933

“Patients taking β-adrenergic blocking agents may be at increased risk when receiving allergen immunotherapy, because β-receptor blockade can make treatment of anaphylaxis more difficult. Therefore, β-adrenergic blocking agents are relative contraindications for immunotherapy.”

Consider glucagon infusion when on board β blockers complicate treatment

- Glucagon activates adenyl cyclase directly and thus bypasses the β-adrenergic receptor

- Glucagon infusion:
  1 to 5 mg administered intravenously over 5 minutes and followed by an infusion (5 to 15 μg/min) titrated to clinical response
  - In children, 20-30 μg/kg (maximum dose, 1 mg)
Consider systemic glucocorticosteroids

- Does not impact the *acute* management of anaphylaxis because they might have no effect for 4 to 6 hours, even when administered intravenously.

- Consider in these patients:
  - Recent use of corticosteroids
  - Asthma history
  - Anaphylaxis is severe and prolonged.
  - Idiopathic anaphylaxis history
Glucocorticosteroid DOSING

- IV glucocorticosteroids should be administered every 6 hours at a dosage equivalent to 1.0 to 2.0 mg/kg/d of methylprednisolone
- Oral administration of glucocorticosteroids (eg, prednisone, 0.5 mg/kg) might be sufficient for less critical anaphylactic episodes
Adult Dosing of Anaphylaxis Medications

- Epinephrine 1:1000, 0.3-0.5 mL IM
- Diphenhydramine 25-50 mg IV/IM
- Ranitidine 50 mg IV/IM
- Methylprednisolone 125 mg IV/IM
- Hydrocortisone 250-500 mg IV/IM
- Dexamethasone 10 mg IV/IM
- Albuterol neb or MDI: dose as for asthma
Cardiopulmonary arrest during anaphylaxis

- PROLONGED AND DEDICATED RESUSCITATION IS ENCOURAGED, IF NECESSARY, BECAUSE EFFORTS ARE MORE LIKELY TO BE SUCCESSFUL IN ANAPHYLAXIS

- Cardiopulmonary resuscitation and ACLS measures
- Cardiac-dose epinephrine administered IV
- Rapid volume expansion
- Atropine and transcutaneous pacing if asystole and/or pulseless electrical activity are present
- Transport to emergency department or intensive care facility, as setting dictates
Observation, transport, follow-up

- Strongly consider transfer to emergency department
- Observation periods and level of monitoring must be individualized and based on such factors as clinical scenario and distance from the patient’s home to the closest emergency facility
- No reliable predictors of biphasic or protracted anaphylaxis on the basis of initial clinical presentation
- After resolution of the acute episode, patients should be provided with an epinephrine syringe and receive proper instruction for self-administration
Equipment that should be available for the treatment of anaphylaxis

- Stethoscope and sphygmomanometer
- Tourniquets, syringes, hypodermic needles, and large-bore (#14) needles
- Injectable aqueous epinephrine 1:1000
- O2 administration set
- IV fluids setup
- Oral airway
- Diphenhydramine or similar injectable antihistamine
- Corticosteroids for intravenous injection
- a vasopressor (eg, dopamine or norepinephrine)
- Glucagon
Other useful equipment
(optional, based on situation)

- An automatic defibrillator
- 1-way valve facemask with an oxygen inlet port (eg, Pocket-Mask or similar device)
- Spirometry
- Pulse oximetry might be useful in patients with dyspnea, bronchospasm, or both.
Preparedness and prevention during allergen immunotherapy

- Consider periodic anaphylaxis practice drills
- The emergency equipment should be up to date and complete
- Patients should wait in clinic for 20 or 30 minutes after receiving an allergen immunotherapy injection
- Consider requiring patients to carry and know how to use injectable epinephrine
Drugs for Patients Who Are Beta Blocked

- Atropine 0.5 mg IV, repeat every 10 minutes
- Glucagon 1-5 mg IV
- Ipratropium neb or MDI: dose as for COPD
Summary

• Know the signs and symptoms of anaphylaxis

• Be prepared, have your office prepared, for the unexpected

• When in doubt, administer epinephrine