Anaphylaxis
Risk Assessment, Use of Epinephrine

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Tampa, Florida
• ASTHMA IS A RISK FACTOR FOR

• ANAPHYLAXIS
Questions

1. How is anaphylaxis defined?
2. Can you predict the seriousness of a reaction by the presenting signs and symptoms?
3. Can you predict the seriousness of the reaction by identifying the route of antigen presentation, parenteral or oral?
4. Can the time of onset predict a more serious reaction?
5. How should epinephrine be administered?
6. When should epinephrine be administered?
7. Is epinephrine safe?
Questions

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7. Is epinephrine safe?
Mechanisms underlying human anaphylaxis. Anaphylaxis might be immune mediated or might occur through direct (nonimmune) perturbation of mast cells. Idiopathic anaphylaxis, currently a diagnosis of exclusion, presents opportunities for elucidation of pathophysiologic mechanisms.

Simons FER. *J Allergy Clin Immunol* 2006;1;17:366-77
Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   **AND AT LEAST ONE OF THE FOLLOWING**

   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
Second NIAID Food Allergy and Anaphylaxis Network Symposium  (cont’d)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

*PEF, Peak expiratory flow; BP, blood pressure.

* Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

When a patient fulfills any of the 3 criteria of anaphylaxis outlined above, the patient should receive epinephrine immediately because epinephrine is the treatment of choice in anaphylaxis. There undoubtedly will be patients who present with symptoms not yet fulfilling the criteria of anaphylaxis yet in whom it would be appropriate to initiate therapy with epinephrine, such as a patient with a history of near-fatal anaphylaxis to peanut who ingested peanut and within minutes is experiencing urticaria and generalized flushing.

• Sampson HA et al. *J Allergy Clin Immunol* 2006;117:391-7
Anaphylaxis in Infants: Can Recognition and Management be Improved?

Anaphylaxis signs in infants: obvious but may be nonspecific

Skin/mucus membranes: rapid onset of hives (potentially difficult to discern in infants with acute atopic dermatitis; scratching and excoriations, as such, will be absent in young infants); angioedema (face, tongue, oropharynx)

Respiratory: rapid onset of coughing, choking, stridor, wheezing, dyspnea, apnea, cyanosis

Gastrointestinal: sudden, profuse vomiting

Cardiovascular: weak pulse, arrhythmia, diaphoresis/sweating, pallor, collapse/unconsciousness

Central nervous system: rapid onset of unresponsiveness, lethargy, or hypotonia; seizures

• Simons FER. J Allergy Clin Immunol 2007;120:537-40
Anaphylaxis from World Allergy Organization: Statement on Epinephrine

• Anaphylaxis is an acute and potentially lethal multisystem allergic reaction in which some or all of the following signs and symptoms occur: diffuse erythema, pruritus, urticaria and/or angioedema; bronchospasm; laryngeal edema; hypotension; cardiac arrhythmias; feeling of impending doom; unconsciousness and shock. Other earlier or concomitant signs and symptoms can include itchy nose, eyes, pharynx, genitalia, palms, and soles; rhinorrhea; change in voice; metallic taste; nausea, vomiting, diarrhea, abdominal cramps, and bloating; lightheadedness; headache; uterine cramps; and generalized warmth.

Kemp SF, Lockey RF, Simons FER, et al. *Allergy* 2008;63:1061-1070
## World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom(s)/sign(s) of 1 organ system present</strong>&lt;sup&gt;*&lt;/sup&gt;</td>
<td><strong>Symptom(s)/sign(s) of more than 1 organ system present</strong>&lt;sup&gt;+&lt;/sup&gt; or</td>
<td><strong>Lower respiratory</strong> Asthma (eg, 40% PEF or FEV&lt;sub&gt;1&lt;/sub&gt; drop) NOT responding to an inhaled bronchodilator) or <strong>Upper respiratory</strong> Laryngeal, uvula, or tongue edema with or without stridor</td>
<td><strong>Lower or upper respiratory</strong> Respiratory failure with or without loss of consciousness or <strong>Cardiovascular</strong> Hypotension with or without loss of consciousness</td>
<td>Death</td>
</tr>
<tr>
<td>Cutaneous Generalized pruritus, urticaria, flushing, or sensation of heat or warmth&lt;sup&gt;†&lt;/sup&gt; or Angioedema (not laryngeal, tongue or uvular) or</td>
<td>Lower respiratory Asthma: cough, wheezing, shortness of breath (eg, less than 40% PEF or FEV&lt;sub&gt;1&lt;/sub&gt; drop, responding to an inhaled bronchodilator) or <strong>Gastrointestinal</strong> Abdominal cramps, vomiting, or diarrhea or <strong>Other</strong> Uterine cramps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory Rhinitis - (eg, sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) or Throat-clearing (itchy throat) or Cough perceived to originate in the upper airway, not the lung, larynx, or trachea or Conjunctival Erythema, pruritus or tearing <strong>Other</strong> Nausea, metallic taste, or headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Worldwide Reporting and Grading System for Anaphylaxis

* This constellation of symptoms may progress rapidly to anaphylaxis; Mild symptoms or signs may progress rapidly to severe anaphylaxis and death.

• Patients may also have a feeling of impending doom, especially in grades 2, 3 and 4.

• Vasovagal symptoms can occur with any medical intervention and should be considered. Vasovagal reactions can be serious and have been associated with death.

Worldwide Reporting and Grading System for Anaphylaxis (cont’d)

- The final grading is not determined until the event is over, regardless of the medications administered.

- Time of onset from the immunotherapy dose and the first sign(s) and symptom(s) should be included as indicated.

Oral allergy syndrome is defined as, “Local IgE-mediated mast cell activation provokes the rapid onset of pruritus, tingling and angioedema of the lips, tongue, palate and throat, and occasionally a sensation of pruritus in the ears and/or tightness in the throat”. It is associated with the oral administration of an allergen. Oral allergy syndrome is not part of this grading system.

Sampson. In: Middleton
1. **How is anaphylaxis defined?**

Answer:

- There are different definitions of anaphylaxis.
- For the clinician, it is better to define anaphylaxis to include any systemic sign or symptom associated with a known or suspected allergen exposure temporally related to its onset.
Questions

1. How is anaphylaxis **defined**?

2. **Can you predict the seriousness of a reaction by the presenting signs and symptoms?**

3. Can you predict the seriousness of the reaction by identifying the route of antigen presentation, parenteral or oral?

4. Can the time of onset predict a more serious reaction?

5. How should epinephrine be administered?

6. When should epinephrine be administered?

7. Is epinephrine safe?
Grading System for Generalized Hypersensitivity Reactions (1149 Cases of Anaphylaxis)  
(Modified by Lockey)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Defined by</th>
<th>% without Skin Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – Mild (skin and subcutaneous tissues only)*</td>
<td>Generalized erythema, urticaria, periorbital edema, or angioedema</td>
<td>0%</td>
</tr>
<tr>
<td>2 – Moderate (features suggesting respiratory, cardiovascular, or gastrointestinal involvement)</td>
<td>Dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain</td>
<td>17%**</td>
</tr>
<tr>
<td>3 – Severe (hypoxia, hypotension, or neurologic compromise)</td>
<td>Cyanosis or ( \text{SpO}_2 \leq 92% ) at any stage, hypotension (SBP &lt; 90 mm Hg in adults), confusion, collapse, LOC, or incontinence</td>
<td>22%**</td>
</tr>
</tbody>
</table>

SBP, Systolic blood pressure,: LOC, loss of consciousness.
* Mild reactions can be further subclassified into those with and without angioedema
** Comment: may have been missed in these
• Brown SGA. *J Allergy Clin Immunol* 2004;114:371-6
Fatal and Near-Fatal Anaphylactic Reactions to Food in Children and Adolescents

• 6 fatal & 7 near fatal
• 5 of 6 fatalities reported oral or abdominal cramps (itching or tingling in the mouth, tightness in the throat, and abdominal cramps or vomiting). One experienced “skin” symptoms. No patient received epinephrine at onset.
• 7 near fatal. All had skin symptoms. No patient received epinephrine when the initial symptoms began.
• Conclusion: the failure to recognize the severity of the reaction and to administer epinephrine promptly increases the risk of fatal outcome.

## Systemic Reactions, Signs and Symptoms from Venom Immunotherapy

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Subjects with each sign or symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=193</td>
<td>N=106</td>
<td>N=38</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pruritus</th>
<th>75 (54%)</th>
<th>31 (29%)</th>
<th>9 (32%)</th>
<th>115</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioedema/urticaria</td>
<td>72 (37%)</td>
<td>33 (31%)</td>
<td>9 (32%)</td>
<td>114</td>
</tr>
<tr>
<td>GI Symptoms</td>
<td>--</td>
<td>0</td>
<td>11 (39%)</td>
<td>11</td>
</tr>
<tr>
<td>Upper airway obstruction</td>
<td>--</td>
<td>63 (59%)</td>
<td>9 (32%)</td>
<td>2</td>
</tr>
</tbody>
</table>

Questions

2. Can you predict the seriousness of a reaction by the presenting signs and symptoms?

Answer:
Cutaneous symptoms and other mild symptoms can be the initial signs and symptoms and are many times associated with serious life-threatening anaphylaxis.
Questions

1. How is anaphylaxis defined?
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4. Can the time of onset predict a more serious reaction?
5. How should epinephrine be administered?
6. When should epinephrine be administered?
7. Is epinephrine safe?
Reaction grade according to etiology
• Brown SGA. J Allergy Clin Immunol 2004;114:371-6
Food Fatalities, 2001-2006

- Epinephrine Given

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>4</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
</tr>
<tr>
<td>No</td>
<td>22  (12 none &amp; 10 too late)</td>
</tr>
</tbody>
</table>

TOTAL 31

- Bock et al. *JACI* 2007
Autopsy Series of Anaphylactic Reactions

- **Conclusion:** Epinephrine given too late, only 14% received it before respiratory arrest

- Median minutes to arrest: 55 iatrogenic, 5 (1 – 80); 37/oral, 30 (6 – 360); 32 venom, 15 (4 – 120)

- Pumphrey RSH. *Clin Exp Allergy* 2000
3. Can you predict the seriousness of the reaction by identifying the route of antigen presentation, parenteral or oral?

Answer:

• Parenteral route potentially more dangerous than oral, but both can be serious and life-threatening.
Questions

1. How is anaphylaxis defined?
2. Can you predict the seriousness of a reaction by the presenting signs and symptoms?
3. Can you predict the seriousness of the reaction by identifying the route of antigen presentation, parenteral or oral?
4. **Can the time of onset predict a more serious reaction?**
5. How should epinephrine be administered?
6. When should epinephrine be administered?
7. Is epinephrine safe?
## Time of Onset of Fatal Reactions from SCIT

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 3 minutes</td>
<td>17</td>
</tr>
<tr>
<td>3 – 10 minutes</td>
<td>11</td>
</tr>
<tr>
<td>10 – 20 minutes</td>
<td>7</td>
</tr>
<tr>
<td>20 – 30 minutes</td>
<td>4</td>
</tr>
<tr>
<td>&gt; 30 minutes</td>
<td>7</td>
</tr>
<tr>
<td>Unknown</td>
<td>12</td>
</tr>
</tbody>
</table>

**TOTAL** 58

- Lockey et al. *JACI* 1987
- Reid, Lockey et al. *JACI* 1993
- Bernstein et al. (Similar questionnaire) 2004
Evaluation of Near-Fatal Reactions to Allergen Immunotherapy Injections (Comparison with Fatal Reactions)

- Epinephrine was delayed for longer than 20 minutes or not administered in 30% of FRs compared with 6% of NFRs (OR, 7.3; 95% CI, 1.4 - 40; P = .01)

Questions

4. Can the time of onset predict a more serious reaction?

Answer:

- More serious reactions tend to have an early onset of signs and symptoms. However, exceptions.
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4. Can the time of onset predict a more serious reaction?
5. **How should epinephrine be administered?**
6. When should epinephrine be administered?
7. Is epinephrine safe?
Absorption of epinephrine is faster after intramuscular injection than after subcutaneous injection. In a prospective, randomized, blinded study in children, the tmax was 8 ± 2 minutes after injection of epinephrine 0.3 mg from an EpiPen intramuscularly in the vastus lateralis. In contrast, the time to tmax was 34 ± 14 minutes (range, 5 to 120) after injection of epinephrine 0.01 mg/kg subcutaneously in the deltoid region. Based on data from Simons et al.

- Simons FER. *J Allergy Clin Immunol* 2004;113:837-44
Questions

5. How should epinephrine be administered?

Answer:

• IM, preferably in the anterior-lateral thigh. Use appropriate doses commensurate with the seriousness of the preventing signs and symptoms.
Questions

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4. Can the time of onset predict a more serious reaction?
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6. **When should epinephrine be administered?**
7. Is epinephrine safe?
Controlled Trials of the Use of Epinephrine for Anaphylaxis

• “… no randomized controlled trials…”

• “adrenaline in anaphylaxis is based on tradition and on evidence from fatalities … from anaphylaxis…” not receiving (SIC) … adrenaline …”

Intramuscular adrenaline is the acknowledged first-line therapy for anaphylaxis, in hospital and in the community, and should be given as soon as the condition is recognized. There are no absolute contraindications to administering adrenaline in children. Absolute indications for prescribing self-injectable adrenaline are prior cardiorespiratory reactions, exercise-induced anaphylaxis, idiopathic anaphylaxis and persistent asthma with food allergy. Relative indications include peanut or tree nut allergy, reactions to small quantities of a given food, food allergy in teenagers, and living far away from a medical facility.

• Muraro A et al. *Allergy* 2007;62:857-71
Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization

• The Committee strongly believes that epinephrine is currently under-utilized and often dosed suboptimally to treat anaphylaxis, is under-prescribed for potential future self-administration, that most of the reasons proposed to withhold its clinical use are flawed, and that the therapeutic benefits of epinephrine exceed the risk when given in appropriate IM doses.

Kemp SF, Lockey RF, Simons FER, et al. Allergy 2008;63:1061-1070
Systemic reactions (SR) to percutaneous (P) and intradermal (ID) skin tests (ST)

Background

• The purpose of this study is to determine over 12 months, 2/1/06-1/31/07:
• Rate of SRs to both P and ID ST
• Symptoms reported
• Response to immediate treatment with epinephrine IM

• Bagg A, Chacko T, Lockey RF. *Ann Allergy, Asthma Immunol* 2009;102(5):400-402
Methods

• A retrospective review over a one year period.
• Evaluate SRs to P and ID ST to 20 to 50 allergens (trees, grasses, weeds, animals, molds, foods, medications, and Hymenoptera)
• 1,456 subjects.
• Nurses as instructed by the attending physicians administered epinephrine 1:1000 v/v, 0.2mL IM as soon as any signs or symptoms of anaphylaxis occurred
Results

- 52 patients (3.5%) had SRs
- 43 (83%) female and 9 (17%) male
- The average age of the patients with SRs was 40.6 years (range 13-70, median 35.5 years)
- 17/52 (33%) had asthma
Results: Symptoms Reported

- pruritic eyes, nose, and/or pharynx (40%)
- worsening cough (27%)
- sensation of difficulty swallowing (17%)
- worsening nasal congestion (15%)
- rhinorrhea (13%)
- chest tightness and/or shortness of breath (13%)
- generalized pruritus (12%)
- sneezing (12%)
- urticaria (4%)
- wheeze (4%)
- no severe asthma, shock, hypotension, unconsciousness, or late phase responses occurred
Treatment

- **52 (100%)** patients received epinephrine (average dose, 0.2 cc, 1:1000 IM)
- **48 (92%)** oral prednisone, **9 (17%)** oral prednisone to take 6 to 8 hours after reaction
- **50 (96%)** oral antihistamine (H1)
- **6 (12%)** nebulized beta agonist.
Summary of ST Reactions

- SRs occurred in 3.5% of patients skin tested and readily responded to early intervention with epinephrine
- This early administration of epinephrine by nurses appears to prevent more serious and late phase reactions
- Similar findings with IT systemic reactions presented at the 2009 AAAAI meeting.
Questions

6. When should epinephrine be administered?

• As soon as any systemic signs or symptoms appear. Use in appropriate doses, IM, commensurate with the severity of the initial signs and symptoms.
1. How is anaphylaxis defined?
2. Can you predict the seriousness of a reaction by the presenting signs and symptoms?
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DBPC Cross-Over of *Myrmecia pilosula* VIT and Purposeful Sting

- 21 SR in placebo group
- 17-first SX generalized pruritus and abnormal perioral sensation (tingling lips or tongue or abnormal taste)
- Erythema with or without urticaria in 3. One “lump in throat”

Skin Features in All

- Generalized erythema, 100%
- Pruritus, 82%
- Uritcaria, 68%

Epinephrine Infusion Given In:

1) 19
2) Two urticarial reactions resolved
3) Age 17-65
4) Epinephrine dose, median IV 590 µg
   (range 190 – 1,310 µg )
5) Infusion duration, median 115 min
   (range 52 – 290 minutes)
6) No side effects reported

• Epinephrine may cause pharmacologic adverse effects such as anxiety, fear, restlessness, headache, dizziness, palpitations, pallor, and tremor. Rarely, and especially after overdose, it may lead to ventricular arrhythmias, angina, myocardial infarction, pulmonary edema, sudden sharp increase in blood pressure, and intracranial hemorrhage. There is, however, no absolute contraindication to epinephrine use in anaphylaxis.

• Simons FER. *J Allergy Clinical Immunol* 2004;113:837-44
Questions

7. **Is epinephrine safe?**
   - Yes, use IM in appropriate doses depending on the severity of the reaction.
## Summary

### PROGNOSIS

<table>
<thead>
<tr>
<th>Factor</th>
<th>Poor</th>
<th>Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of antigen (allergen)</td>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>Onset of symptoms</td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>Initiation of treatment</td>
<td>Late</td>
<td>Early</td>
</tr>
<tr>
<td>Route of exposure</td>
<td>Parenteral</td>
<td>Oral*</td>
</tr>
<tr>
<td>Beta-adrenergic blocker use</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Presence of underlying disease</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* True for drugs, not foods
Physician-Supervised Management of Anaphylaxis

I. Epinephrine

a) Epinephrine IM in thigh (0.3 mg – 0.5 mg)

b) Repeat as necessary while monitoring response

c) Epinephrine repeated as often as necessary to control symptoms of anaphylaxis (0.01 mg/kg for children or
d) Aqueous epi 1:1000, 0.1-0.3ml in 10ml NS (1:100,000 to 1:33,000 dilution), IV over several min prn.

e) For potentially moribund subjects, tubercular syringe, EPI, 1:1000, 0.1 ml, insert into vein or IV, aspirate 0.9 ml of blood or NS (1:10,000 dilution). Give as necessary for response.
II. General measures

a) Place in recumbent position and elevate lower extremities.

b) Maintain airway (endotracheal tube or cricothyrotomy).

c) O₂, 6-8 liters/min.

d) NS IV. If severe hypotension, give vol expanders (colloid sol).

e) Venous tourniquet above reaction site. Question decreases absorption of allergen.
Specific Measures that Depend on Clinical Scenario

a) Aqueous EPI 1:1,000, ½ dose (0.1-0.2 mg) at reaction site.

b) Diphenhydramine, 50 mg or more in divided doses orally or IV, maximum daily dose 300 mg (5 mg/kg) for children and 400 mg for adults.

c) Ranitidine, 50 mg in adults and 12.5-50 mg (1 mg/kg) in children, dilute in 5% G/W, total 20 ml, inject IV, over 5 min. (Cimetidine 4 mg/kg OK for adults, not established for pediatrics).
Specific Measures that Depend on Clinical Scenario  (cont’d)

d) Bronchospasm, nebulized albuterol 2.5-5 mg in 3 ml NS or levalbuterol 0.63-1.25 mg as needed.

e) Aminophylline, 5mg/kg over 30 min IV may be helpful. Adjust dose based on age, medications, disease, current use.

f) Refractory hypotension, dopamine, 400 mg in 500 ml G/W. IV 2-20 mcg/kg/min more or less.
Specific Measures that Depend on Clinical Scenario (cont’d)

g) Glucagon, 1-5 mg (20-30 mcg/kg [max 1 mg] in children), administered IV over 5 min followed with IV infusion 5-15 mcg/min.

h) Methylprednisolone, 1-2 mg/kg per 24 hr, prevents prolonged reactions and relapses.
Conclusions

• Physicians and other health care professionals should be instructed to give appropriate doses of epinephrine at the earliest signs of anaphylaxis.
• This is particularly true if the allergen is parenteral.
• The risk/benefit of giving epinephrine outweighs the risk of not giving it.
Thank you!
Anaphylaxis Defined

- A generalized or systemic hypersensitivity reaction, most commonly but not always IgE mediated, but where mast cell and basophil mediators play predominant role, which is
  - rapid in onset
  - potentially life-threatening
  - almost always unanticipated
- Initial mild symptoms may progress to a severe and irreversible outcome

PRIMARY SYMPTOMS OF ANAPHYLAXIS

- **SKIN:** flushing, itching, urticaria, angioedema
- **Gastrointestinal:** nausea, vomiting, bloating, cramping, diarrhea
- **Gynecologic**
  - Uterine Cramping
- **Other**
  - Feeling of impending doom
  - Metallic taste
- **RESPIRATORY:**
  - dysphonia, cough, stridor, wheezing, dyspnea, chest tightness, asphyxiation, death
- **CARDIOVASCULAR:**
  - tachycardia, hypotension, dizziness, syncope, death

2. Phillip Korenblat, MD. Professor, Internal Medicine, Washington
ANAPHYLAXIS OBSERVATIONS
SIGN AND SYMPTOMS

- Skin symptoms most common (> 90% of patients)
- Skin, oral, and throat symptoms often first noted
- Respiratory symptoms: 40% to 70% of patients
- Gastrointestinal symptoms: about 30% of patients
- Shock: about 10% of patients
- Signs and symptoms: usually within 5 to 30 minutes
- More rapid the onset, the more serious the reaction

Anaphylaxis Epidemiology

- No racial or ethnic differences
- Anaphylaxis more common in children and adolescents
- Anaphylactic DEATHS more common in adults
- M>F to age 15  Then F>M for > 15
- Males:Hymenoptera
- Females: Latex, ASA/NSAIDS, Muscle relaxants
- Atopy: for Foods, RCM, Latex, EIA, Idiopathic  
  But not for Hymenoptera,  PCN, Insulin
- Oral less likely/ severe than systemic (Drugs)
- Gaps in administration predispose to reactions  
  but longer interval⇒less likely recurrence
EPIDEMIOLOGY OF ANAPHYLAXIS

• **At Risk:** 1% to 15% of US population (3.3 to 41 million people\(^1\): (30/100,000 population/year)\(^2\)

• **Fatalities** per year in the US:
  - Food-induced: 150
  - Antibiotic-induced: 600
  - Venom-induced: 50

• **Estimated that > 1.21% of the population may be affected**
  – Annual Incidence: 21/100,000\(^2\) **UNDERDIAGNOSED**

• **Food allergy** affects up to 6%-8% of children younger than 4 years of age and 2% of the US population beyond the 1\(^{st}\) decade of life\(^3,4\)

• **Incidence of anaphylaxis** is **increasing**\(^5\)

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Anaphylaxis: Underestimated and Misdiagnosed

Underestimated:
- Negative autopsy findings in fatal reactions
- Rapid death may leave no characteristic macroscopic findings
- Myocardial ischemia is common in anaphylaxis - can be misclassified as death due to Myocardial Infarction

Misdiagnosis / Confusion with other conditions:
- Acute Asthma
- Airway obstruction with foreign body
- Diabetic, septic or other types of shock
- Panic attacks
- Urticaria

Anaphylaxis

Immunologic
- IgE, FcεRI
  - foods, venoms, latex, drugs
- Other
  - blood products, immune aggregates drugs

Idiopathic

Non-Immunologic
- Physical
  - Exercise, cold
- Other
  - drugs

Other

Simons FER. JACI 2006
GELL AND COOMBS CLASSIFICATION OF HYPERSENSITIVITY REACTIONS

<table>
<thead>
<tr>
<th>Type</th>
<th>Classification</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>IMMEDIATE HYPERSENSITIVITY</td>
<td>Anaphylaxis can occur through Types I, II and III</td>
</tr>
<tr>
<td>Type II</td>
<td>CYTOXIC REACTIONS</td>
<td>(Incompatible blood transfusions: complement fixing Abs to formed elements of blood)</td>
</tr>
<tr>
<td>Type III</td>
<td>IMMUNE COMPLEX REACTIONS</td>
<td>(Complement activated by Ag/Ab or molecular aggregates: IVIG if IgA↓, protamine, dextran)</td>
</tr>
<tr>
<td>Type IV</td>
<td>DELAYED HYPERSENSITIVITY</td>
<td></td>
</tr>
</tbody>
</table>
Anaphylactic Triggers

Based on summary of published studies:
In many reactions, anaphylactic triggers are unknown

Golden. *Anaphylaxis* 2004
Fatal Reactions Etiology


- Sting: 47
- Anesthetic: 35
- Nuts: 32
- Antibiotics: 27
- Possible Food: 18
- Other Drug: 15
- Food: 13
- Contrast Media: 11
- Other: 3

Pumphrey RSH. Anaphylaxis 2004
UK ANAPHYLAXIS DEATH REGISTER (Pumphrey)

• Main findings
  • ~20 recorded deaths/year i.e. ~1:2.8 million
  • 50% iatrogenic; 25% food and 25% venom
  • ~50% died from asphyxia (food) and 50% from shock (iatrogenic and venom)
  • Median time to death:
    5 mins if iatrogenic; 15 mins venom; and 30 mins food
  • Adrenalin rarely used before cardiac arrest

Fatal Anaphylactic Reactions

Fatal anaphylactic reactions are often associated with:

- Delay between time of symptom onset and administration of treatment\(^1\)
- History of asthma\(^1,2\)
- Adverse events due to medication\(^2\)

However, most fatal reactions are unpredictable

- Appropriate management after recovery from a severe reaction may be protective against a fatal recurrence\(^2\)
- Epinephrine is used in treatment of 62% of fatal reactions, but given before cardiac arrest in only 14% of reactions\(^3\)

AGENTS THAT CAUSE ANAPHYLAXIS: IgE-DEPENDENT TRIGGERS

- foods (e.g., peanut, tree nuts, seafood)
- medications (e.g., β-lactam antibiotics)
- venoms
- latex
- allergen immunotherapy
- diagnostic allergens
- exercise (with food or medication co-trigger)
- hormones
- animal or human proteins
- colorants (insect-derived, e.g., carmine)
- enzymes
- polysaccharides
- aspirin and NSAIDs (possibly through IgE)

Kemp SF and Lockey RF, J Allergy Clin Immunol 2002;110:341-8
Triggers of Anaphylaxis: Food

- Peanuts
- Shellfish
- Tree nuts (e.g., walnuts, pecans)
- Milk
- Eggs
- Fish
- Wheat
- Soybean
FATAL FOOD-INDUCED ANAPHYLAXIS

A clinical review of anaphylactic fatalities (N=32)

- In a retrospective analysis of 32 deaths in patients age 2-33 years
  - Peanut and tree nuts caused >90% of reactions
  - Prevalence of peanut allergy has doubled in children <5 years of age in the last 5 years
  - Most patients had a history of asthma
  - Most did not have injectable epinephrine available at the time of their reaction and death

IATROGENIC ANAPHYLAXIS

• Estimated 550,000 serious allergic reactions to drugs/year in US hospitals
• Most common drug triggers
  - Penicillin (highest number of deaths from anaphylaxis)
  - Sulfa drugs
  - Non-steroidal anti-inflammatory drugs
  - Muscle relaxants
• Most common biologic triggers
  - Anti-sera for snakebite
  - Anti-lymphocyte globulin
  - Vaccines
  - Allergens

Neugut AI et al. Arch Intern Med 2001;161:15-21
Anaphylactic Triggers: Adverse Therapeutic Events

• **Medications**
  – Antibiotics (especially penicillin)
  – Aspirin and other NSAIDs
  – Cancer chemotherapeutic agents
  – Anesthetics (suxamethonium, veroconium)

• **Diagnostic Agents**
  – Iodinated contrast media
  – Fluorescein

• **Blood transfusions**

• **Allergen immunotherapy**

• **Vaccinations**
  – Anti-venoms
  – Monoclonal antibodies
PERI-OPERATIVE ANAPHYLAXIS

- Neuromuscular blocking drugs (muscle relaxants), e.g., suxamethonium, rocuronium, alcuronium, atracurium
- Induction agents, e.g., thiopentone, propofol, alfathesin
- Other: including local anesthetics, antibiotics, protamine, and latex
- Predisposing factors: atopy, asthma; previous exposure

Fisher M. In: Anaphylaxis, John Wiley & Sons Ltd., Chichester, UK, 2004:193-206
ALLERGEN IMMUNOTHERAPY – INDUCED ANAPHYLAXIS

• Fatal reactions uncommon: 1 per 2,000,000 injections
• Risk factors for fatality include:
  - Dosing errors
  - Poorly controlled asthma (FEV₁ < 70%)
  - Concomitant β-blocker use
  - Lack of proper equipment and trained personnel
  - Inadequate epinephrine treatment

Stewart GE and Lockey RF. J Allergy Clin Immunol 1992;90:567-78
Triggers of Anaphylaxis: Insect Stings and Bites

• Bees
• Vespids
  Wasps
  Yellow Jackets
  Hornets
• Fire ants

At least 50 deaths per year in US (0.5% - 5% Allergic)-- Rising

↑ numbers of fire ants and Africanized bees and ↑ outdoor activity
Hymenoptera insects

- wasp
- fireant
- Honey bee
- Yellow jacket
Triggers of Anaphylaxis: Latex

• Some groups are at increased risk
  – Healthcare workers (11-15%)
  – Children with spina bifida (up to 50%)
  – Persons having 3 or more surgeries
  – Otherwise < 1% population

• Incidence has decreased since powder-free latex gloves and non-latex gloves have become available

FOOD-DEPENDENT EXERCISE-INDUCED ANAPHYLAXIS

• Most common in females, and from late teens to mid-30’s
• Triggered by exercise 2-4 hours after ingesting offending food
• Foods implicated: wheat, seafood, fruit, milk, celery and fish.
• Associations: asthma, positive skin prick tests to foods
• Mechanism: two signals required

Aunhachoke K et al. J Med Assoc Thai 2002;85:1014-8
ANAPHYLAXIS FROM IMMUNE CAUSES OTHER THAN IgE

• Cytotoxic (Type II)
  - transfusion reactions to cellular elements (IgG, IgM)

• Immune aggregates (Type III)
  - intravenous immunoglobulin
  - Dextran (possibly)

Kemp SF and Lockey RF, J Allergy Clin Immunol 2002;110:341-8
ANAPHYLAXIS: NON-IMMUNOLOGIC CAUSES

MULTIMEDIATOR COMPLEMENT ACTIVATION/ACTIVATION OF CONTACT SYSTEM

- Radiocontrast media
- Ethylene oxide gas on dialysis tubing (possibly through IgE)
- Protamine (possibly)
- ACE-inhibitor administered during renal dialysis with sulfonated polyacrylonitrile, cuprophane, or polymethylmethacrylate dialysis membranes

Kemp SF and Lockey RF. J Allergy Clin Immunol 2002;110:341-8
ANAPHYLAXIS: NON-IMMUNOLOGIC CAUSES

NONSPECIFIC DEGRANULATION OF MAST CELLS AND BASOPHILS

- Opiates
- Physical factors:
  - exercise (no food or medication co-trigger)
  - temperature (cold, heat)

Kemp SF and Lockey RF, J Allergy Clin Immunol 2002;110:341-8
IDIOPATHIC ANAPHYLAXIS

• Common in adults referred to allergists for anaphylaxis
• Uncommon in children
• Negative skin tests, negative dietary history, no associated diseases eg. mastocytosis
• Preventive medication: oral corticosteroids, $H_1$ & $H_2$ antihistamines, anti-leukotrienes
• Deaths rare
• May gradually improve over time

**BIPHASIC/LATE-PHASE REACTION**

Cellular infiltrates: 3 to 6 hours (LPR)

- **Eosinophil**
  - CysLTs, GM-CSF, TNF-α, IL-1, IL-3, PAF, ECP, MBP

- **Basophil**
  - Histamine, CysLTs, TNF-α, IL-4, IL-5, IL-6

- **Monocyte**
  - CysLTs, TNF-α, PAF, IL-1

- **Lymphocyte**
  - IL-4, IL-13, IL-5, IL-3, GM-CSF

**Allergen**
- Histamine, IL-4, IL-6
- PGs
- CysLTs
- Proteases

**Mast cell**
- EPR 15 min (Early-Phase Reaction)
  - 3 to 6 hours (CysLTs, PAF, IL-5)

**Return of Symptoms**
Anaphylactic Reaction

Mast Cell

Allergen

IgE antibody

Mast cell granules

Immediate reaction
- Wheeze
- Urticaria
- Hypotension
- Abdominal cramping

Late-phase reaction
ACUTELY RELEASED MEDIATORS OF ANAPHYLAXIS

- Degranulation of mast cells and basophils causes the release of:
  - preformed granule-associated substances
    - histamine
    - heparin
    - tryptase
    - chondroitin sulfate
    - chymase
    - carboxypeptidase
  - cytokines
  - newly-generated lipid-derived mediators
    - prostaglandin D$_2$
    - leukotriene (LT) B$_4$, LTC$_4$, LTD$_4$, LTE$_4$
    - platelet activating factor.

↓ PAF acetylhydrolase and/or ↓ histamine deaminase ⇒ ↑RISK

Kemp SF and Lockey RF. J Allergy Clin Immunol 2002; 110:341-8
Mediator Recruitment

Mast Cell

- Activation of factor XII
  - Clotting
  - Clot lysis
    - Platelet Activation
  - Contact system
    - With kinin formation
  - Complement activation
# Mast Cell and Basophil Mediators

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Pathophysiology</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kininogenase kallikrein</td>
<td>Activate contact system</td>
<td>Hypotension angioedema</td>
</tr>
<tr>
<td>Tryptase</td>
<td>Activate contact system, complement, clotting</td>
<td>Hypotension angioedema, DIC</td>
</tr>
<tr>
<td>Heparin</td>
<td>Inhibits clotting, anticomplementary</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Chymase</td>
<td>Formation angiotensin II</td>
<td>Modulates hypotension</td>
</tr>
</tbody>
</table>
Pathophysiology

• Signs and symptoms due primarily to\(^1\)
  – Smooth muscle contraction
  – Increased vascular permeability
  – Vasodilation

• Respiratory compromise and cardiovascular collapse cause most fatalities\(^2\)

• Urticaria and angioedema: most common manifestations
  – Might be delayed or absent in rapidly progressive anaphylaxis\(^2\)
  – The more rapid the occurrence, the more likely a severe and life-threatening reaction

• Symptoms generally appear within minutes but can occur as late as several hours\(^2\)

1. Lieberman P. Clinician’s Manual on Anaphylaxis 2005
Endogenous Compensatory Mechanisms for Hypotension

ACE

Phil Lieberman: Anaphylaxis, a clinician’s manual
Multimediator Recruitment in Anaphylaxis

- **Complement**
  - Decreased $C_4$, $C_3$
  - Formation $C_{3a}$

- **Contact system**
  - Decreased high molecular weight kininogen
  - Formation of activation complexes

- **Coagulation pathway**
  - Decreased factor V, VII
  - Decreased fibrinogen
Drugs That May Complicate Rx

- Beta blockers
- Ace inhibitors
- Ace blockers
- Tricyclics
- MAO inhibitors
Patterns of Anaphylaxis

- **Uniphasic**
  - Event that occurs then subsides within 1 to 2 hours after onset of symptoms either with or without therapy\(^1\)

- **Biphasic**
  - Symptoms resolve after treatment but return between 30 minutes and 72 hours later\(^2\)

- **Protracted**
  - Symptoms do not resolve with treatment and may last up to 32 hours despite aggressive treatment\(^3\)

---

Uniphasic Anaphylaxis

- Antigen Exposure
- Initial Symptoms
- Treatment

Time

0
Biphasic Anaphylaxis

Time

Antigen Exposure

0

30 minutes to 72 hours

Classic Model

8 to 12 hours

New Evidence

Initial Symptoms

Second-Phase Symptoms

Treatmetn

Protracted Anaphylaxis

Initial Symptoms

Antigen Exposure

0

Time

Up to 32 hours

**Biphasic Reactions**

- 1% to 20% of attacks\(^1\)
- In up to **one third of patients** with (food induced) fatal or near fatal reactions\(^2\)
- Usually, initial symptomatic period followed by an asymptomatic period of 1 to 8 hours, but the asymptomatic phase may last longer than 24 hours\(^3\)
- No predictive characteristics (age, gender)\(^4\)

---

3. Lieberman P. *Ann Allergy Asthma Immunol* 2005
BIPHASIC AND PROTRACTED ANAPHYLAXIS

- Biphasic anaphylaxis: Return of symptoms after resolution of initial symptoms, without subsequent allergen exposure
  - Symptoms return within 1 to 8 hours (sometimes longer)
  - Up to 20% of anaphylactic reactions are biphasic
  - Patients often require additional epinephrine
- Protracted anaphylaxis: symptoms may be continuous for 5-32 hrs (Requires additional epinephrine)

Biphasic Reactions
Factors signaling a potential 2nd reaction

- A delay of 30 minutes or more between antigen and onset of symptoms\(^1\)
- Ingested antigen\(^2\)
- Severity of first phase\(^2\)
- Hypotension in first phase\(^4\)
- Delay in administration of epinephrine\(^2,3\)
- Failure to give epinephrine or insufficient dose\(^3\)
- Failure to administer or diminished doses of corticosteroid\(^1\)

1. Lieberman P. Ann Allergy Asthma Immunol 2005
2. Lee and Greenes, Pediatrics 2000
3. Lieberman P. Allergy Clin Immunol Int 2004
Subsequent Reactions May Increase in Severity with Time

Severity of previous reaction is not predictive of fatality

* p<0.001

Modified from Simons et al, J Allergy Clin Immunol 2004
LABORATORY TESTS IN THE DIAGNOSIS OF ANAPHYLAXIS

- Plasma histamine
- Serum tryptase
- 24-hr Urinary histamine metabolite
Tryptase and Histamine

- Serum tryptase peaks 60 to 90 minutes after onset of symptoms and can remain elevated as long as 5-6 hours.
- Plasma histamine begins to rise in 5 minutes but remains elevated only 30 to 60 minutes.
- Urinary histamine metabolites may remain elevated as long as 24 hours.
- Under ideal conditions, the positive predictive value of a serum tryptase can be 92.6%, but the negative predictive value is only 52%.

Anesthesiology 99:536,2003
SERUM TRYPTASE

- Histamine and tryptase levels may not correlate
- Tryptase higher if allergen administered parenterally (hymenoptera or injections) than orally (foods)
- Tryptase: Connective tissue mast cells > Mucosal mast cells (MC degranulation $\Rightarrow$ $\beta$ tryptase)
- Ratio Total Tryptase($\alpha + \beta$) / $\beta$ < 10: Anaphylaxis
  - If > 20 indicates systemic mastocytosis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Poor Prognosis</th>
<th>Good Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of symptoms</td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>Initiation of treatment</td>
<td>Late</td>
<td>Early</td>
</tr>
<tr>
<td>Route of exposure</td>
<td>Injection</td>
<td>Oral*</td>
</tr>
<tr>
<td>β-adrenergic blocker use</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Presence of underlying disease</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* true for drugs, not foods
• **Epinephrine** is the drug of choice for all anaphylactic episodes

• Early and aggressive use to maintain airway, blood pressure, and cardiac output

• Flexibility in dosing needed to treat effectively
  – 25% to 35% of patients require more than a single injection
  – Different doses for pediatrics and adults

Lieberman et al. *J Allergy Clin Immunol* 2005
Epinephrine Dosing

• Intramuscular injection in lateral thigh produces most rapid rise in blood level
  – 0.01 mg/kg in children
  – 0.3 to 0.5 mg in adults

• **Drug of choice**
  - Best location is IM in the thigh
    - EpiPen IM thigh 12,222* pg/mL vs Epi IM deltoid 1821 and Saline IM deltoid 1458

• **Used at 1st sign of systemic reaction**
  - The earlier in the allergic process the better the prognosis; delayed use associated with fatal reactions

• **Dose**
  - 0.15mg (33 lbs to 66 lbs); 0.3mg (>66lbs) of a 1:1,000 dilution IM in lateral thigh prn q 5-15 min.
Epinephrine Administration
Epinephrine
Ampule/Needle/Syringe

- EpiPen not available in many countries
- Fixed dose, expensive cost of EpiPen
- Unstable chemical, degrades rapidly by air and light

Needle length 1.27-1.3 cm (No26,27)
EpiPen is 1.43 cm

Instruction to use EpiPen
Epinephrine Use: growing in developed countries

- Awareness is increasing
  - Due largely to increase in awareness of childhood food allergies
- Increased population at risk as number of children with food allergies increases
- Second dose of epinephrine may be required more often than previously suspected

Kemp AS. J Paediatr Child Health, 2003
Epinephrine Use: not available in all countries

A WAO House of Delegates survey (2003 to 2005) in 35 countries

Simons FER. Ann Allergy Asthma Immunol 2005
Causes of Epinephrine failure

- Delayed administration
- Rapid progression of anaphylaxis
- Inadequate doses
- Inappropriate route
- Use of expired epinephrine
- Underlying disease eg. asthma, CVD
- Patient taking a beta-blocker
Expired Epinephrine Content
Percent of Labeled dose

Simons FER et al. JACI 2000;105:1025
Epinephrine is Underutilized for acute treatment

- Only about 30% of individuals requiring epinephrine during a reaction actually received it\(^1\)
- In fatal food-induced reactions, failure to use, delayed use, or inappropriate dose are contributing factors to death\(^2\)
- Used in treatment of 62% of fatal reactions but given before cardiac arrest in only 14% of reactions\(^3\)

Patients requiring a 2nd dose

Korenblat et al. Allergy Asthma Proc 1999
Varghese et al. AAAAI 2006
Webb et al. J Allergy Clin Immunol 2004
Haymore et al. Allergy Asthma Proc 2005
Kelso JM. J Allergy Clin Immunol 2006
ANAPHYLAXIS IN THE EMERGENCY DEPARTMENT

- Chart review in 21 North American Emergency Departments
- Random sample 678 charts of patients with food allergy
- **Management:**
  - 72% received antihistamines
  - 48% received systemic corticosteroids
  - 16% received epinephrine (24% of those with severe reactions)
  - 33% received inhaled albuterol
  - only 16% received Rx for self-injectable epinephrine
  - only 12% referred to an allergist

Clark S et al. J Allergy Clin Immunol 2004;347-52
OFFICE MANAGEMENT OF ANAPHYLAXIS
CHECKLIST

• stethoscope and sphygmomanometer
• tourniquets, syringes, needles (including large bore 14-gauge)
• injectable epinephrine (adrenaline) 1:1000
• oral airway and endotracheal tubes
• oxygen, and equipment to administer it
• diphenhydramine (or similar) injectable antihistamine
• corticosteroids for IV injection
• vasopressor (eg dopamine, noradrenaline)
• glucagon
• automatic defibrillator
MANAGEMENT OF ANAPHYLAXIS

I. Speed is critical:
   a) assess airway, breathing, circulation, and mentation
   b) **EPINEPHRINE**, IM into the muscle of the anterolateral thigh;

   1:1000 dilution, 0.3 - 0.5 mL (0.01 mg/kg in children);
   repeat, every 5-15 minutes as necessary.

MANAGEMENT OF ANAPHYLAXIS

II. Secondary measures:
   a) place patient in recumbent position and elevate his/her legs
   b) maintain airway (endotracheal tube or cricothyrotomy)
   c) oxygen, 6 - 8 liters/minute
   d) normal saline IV; volume expanders (colloid solution) for severe hypotension

Kemp SF and Lockey RF. J Allergy Clin Immunol 2002;110:341-8
PHYSICIAN-SUPERVISED MANAGEMENT OF ANAPHYLAXIS

III. Other measures:

a) epinephrine 1:1000, ½ dose (0.1- 0.2 mg) into reaction site
diphenhydramine, 50 mg IV or orally (1.25 mg/kg, up to 50 mg dose for children); maximum daily dose: adults 400 mg; children 200 mg

b) ranitidine, 50 mg in adults and 12.5 - 50 mg (1 mg/kg) in children, dilute in 5% D/W, total 20 ml, inject slowly IV, over 5 minutes (cimetidine 4 mg/kg OK for adults, dose not established for children)
PHYSICIAN-SUPERVISED MANAGEMENT OF ANAPHYLAXIS

• for bronchospasm
  - nebulized albuterol (salbutamol) 2.5 - 5 mg in 3 ml normal saline

• for refractory hypotension
  - dopamine, 400 mg in 500 ml normal saline IV 2 - 20 µg/kg/min
  - glucagon, 1- 5 mg (20 - 30 µg/kg, max 1 mg in children), IV over 5 minutes followed with continuous IV infusion 5-15 µg/min
  - methylprednisolone, 1- 2 mg/kg per 24 hr

Kemp SF and Lockey RF. J Allergy Clin Immunol 2002;110:341-8
Conclusions

• Anaphylaxis is a life-threatening acute reaction which, although increasing in prevalence is frequently misdiagnosed, under-reported and under-treated

• Physician and patient awareness must be increased to properly prevent, diagnose, and treat anaphylaxis and improve patient outcomes.

• Rapid and proper administration of epinephrine is the standard of treatment

• Patients who self administer should be directed to the ER for follow-up care after the first dose of epinephrine

• Recognition that many patients will require a second dose of epinephrine is essential
THANK YOU
• OPTIONAL SLIDES
Clinicians and Patients Need to Improve Action/Treatment Plans¹

- 29 patients interviewed to identify physician advice related to implementation of action plans for severe food allergies
- 85% of patients said that doctors told them to include antihistamines in the treatment of future reactions:
  - 9/21 (43%) have used their epinephrine auto-injector subsequently
  - 7/29 (24%) were told to use antihistamines as the sole treatment, and 6/29 (21%) before using epinephrine

¹ Kong et al. FAAN abstract. 2006.
Clinicians and Patients Need to Improve Action/Treatment Plans¹

- Out of 20 patients with a reported plan of action for future severe reactions, only 45% would use epinephrine, 55% would go to an emergency department, and 70% would take antihistamines.
- Patients report a lack of training regarding the use of EAIs by their doctors, in addition to an emphasis on antihistamine use, which may be reflected in the low planned use of EAIs in future severe allergic reactions.

¹ Kong et al. FAAN abstract. 2006.
Patients and Clinicians Must Increase Awareness of Anaphylaxis and Its Treatment

- 25 patients identified through a 4-year retrospective chart review were surveyed
- Healthcare providers also queried
- Only 18% of patients would seek emergency assistance after using epinephrine
- 59% of patients carried an injector at all times
- 20% would administer epinephrine after an asymptomatic exposure

Adolescents/Young Adults at Risk

• A Web-based questionnaire of 174 participants sought to identify why adolescents are at high risk for fatal food anaphylaxis

• Risk-taking involved
  – Only 74% always carried epinephrine
  – 75% always read labels
    • 42% of these would eat a food labeled “may contain” an allergen

• 29 participants (17%) were designated as “high risk” because they did not always carry epinephrine and ate food that may have contained an allergen

• The education of teens and their peers during social activities may reduce risk-taking and its consequences

Patients Carrying Epinephrine

- A study by Lieberman found that caregivers of children age 0-9 and people 60-70 years of age are more likely to keep their injector with them\(^1\)
- Teenagers and young adults often do not carry their injectors\(^1\)
- A separate study found that only 16% of EpiPen\textsuperscript{®} patients always carry 2 injectors\(^2\)

1. Phil Lieberman, MD. Chief Editor, Joint Task Force on Practice Parameters.
Awareness Must Increase

• Anaphylaxis is a life-threatening acute reaction which is underreported, frequently misdiagnosed, and undertreated
  – Food allergy affects up to 6%-8% of children younger than 4 years of age and 2% of the US population beyond the 1st decade of life\textsuperscript{1,2}
• Rapid and proper administration of epinephrine is the standard of treatment\textsuperscript{2}
  – Many patients require a second epinephrine injection to treat anaphylaxis\textsuperscript{3}

Patients Must Be Educated

- Many patients fail to correctly recognize and treat anaphylaxis
  - Inadequate treatment (often carry 0 or 1 dose of epinephrine)\(^1\)
  - Delay in treatment
  - Failure to use auto-injector properly
  - Outdated epinephrine

Physicians Must Respond

• Many physicians often fail to correctly recognize and treat anaphylaxis
  – Failure to look for biphasic reaction and provide appropriate treatment\(^1\)
  – Delayed treatment\(^1\)
  – Many patients sent home without a referral to an allergist/immunologist or instructions to avoid the allergen\(^2\)
  – Many patients sent home without an epinephrine auto-injector for future reactions or for potential biphasic reaction\(^2\)

Anaphylaxis Is a Growing Public Health Issue

• Measures must be put in place to reduce the risk of accidental exposure and to respond appropriately in an emergency
  – Comprehensive school board policies
  – Standardized school anaphylaxis plans
  – Greater community support and involvement
    • All those in regular contact with children at risk should participate in training sessions
Final Thoughts

• Awareness levels are key to properly preventing, diagnosing, and treating anaphylaxis

• Improved treatment is needed:
  - Flexibility of dosage (0.1, 0.15, 0.3, 0.5) to allow smaller dose for very young and larger dose for bigger adults
  - Flexibility in needle size to assure IM delivery
  - Longer shelf/storage life
  - Smaller device
  - Better labeling

• Patient should be directed to the ER for follow-up care after the first dose of epinephrine for the treatment of anaphylaxis