WHAT’S NEW IN ANAPHYLAXIS?

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Speaker Disclosure

• None
Anaphylaxis

“The most aberrant example of an imbalance between the cost and benefit of an immune response.”


Objectives

• Recognize the signs and symptoms of anaphylaxis, including atypical presentations

• Discuss the pathophysiology of anaphylaxis and what diagnostic tools are available

• Discuss key aspects of anaphylaxis treatment and prevention

• Recognize risk factors for fatal anaphylaxis
Case presentations

• Case #1

A 16 y/o male, with a history of near-fatal anaphylaxis to peanut, accidentally eats a peanut butter cookie. Fortunately for him, he’s standing on the sidewalk outside of your Emergency Room. Within 5 minutes of eating the cookie, he develops acute flushing and hives. He walks into the ED and asks for assistance. Is this anaphylaxis? Should he receive epinephrine?

• Case #2

A 16 y/o male walks into the emergency room with urticaria and wheezing. You diagnose anaphylaxis and inquire about potential triggers. He had a steak sandwich for lunch about 5 hours ago, shortly after returning from his recent camping trip. He’s not sure about tick exposures. Otherwise, there are no other new food exposures, new medications, insect bites, or travel. He’s otherwise been in good health. What’s the probable cause?

Outline

• Defining anaphylaxis
• Incidence and prevalence
• Causes of anaphylaxis
• Pathophysiology
• Clinical manifestations
• Differential Diagnosis
• Diagnostic work-up
• Acute treatment
• Fatal anaphylaxis
• Prevention of future episodes
A practical definition

“Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death.”


Criteria #1

Acute onset of an illness (minutes-several hours) with involvement of the skin, mucosal tissue, or both

AND

at least one of the following:
   a. Respiratory compromise
   b. Reduced blood pressure or associated symptoms of end organ dysfunction

Criteria #2

Two or more of the following that occur rapidly after exposure to a likely allergen for that patient:

a. Involvement of the skin-mucosal tissue
b. Respiratory compromise
c. Reduced blood pressure or associated symptoms
d. Persistent gastrointestinal symptoms


Criteria #3

- Reduced blood pressure after exposure to a known allergen for that patient

Validation of diagnostic criteria in the emergency room

• Sensitivity of 96.7%
• Specificity of 82.4%
• Positive predictive value of 68.6%
• Negative predictive value of 98.4%


Recall Case #1…

• A 16 y/o male with a history of a near-fatal reaction to peanut. Fortunately for him, he's standing outside of your Emergency Room. Within 5 minutes of eating the peanut butter cookie, he develops acute flushing and hives. He walks into the ED and asks for assistance. Initial vital signs are normal.

• Does this patient meet the diagnostic criteria for anaphylaxis?
  • No

• Should this patient receive intramuscular epinephrine?
  • Yes

“There will undoubtedly be patients who present with symptoms not yet fulfilling criteria for anaphylaxis, yet in whom it would be appropriate to initiate therapy with epinephrine”

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Incidence based on dispersion of epinephrine

- Approximately 1% of the population had epinephrine dispensed for out of hospital treatment

Incidence

- The exact incidence is unknown
- An expert panel concluded:
  - Incidence is 50-2000 episodes per 100,000 person-years
  - Lifetime prevalence of 0.05%-2%
- Regardless of actual incidence, it is certain that anaphylaxis is increasing, especially in industrialized counties

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Causes

<table>
<thead>
<tr>
<th>Causes</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foods</td>
<td>Peanut, tree nuts, fish, shellfish, milk and egg</td>
</tr>
<tr>
<td>Drugs</td>
<td>NSAID’s, antibiotics, vaccines, chemotherapy, monoclonal agents, perioperative agents, radiocontrast media</td>
</tr>
<tr>
<td>Insect stings</td>
<td>Wasps, bees, fire ants</td>
</tr>
<tr>
<td>Latex</td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
</tr>
</tbody>
</table>
Causes of anaphylaxis in pediatric population

- **Foods**: 71%
- **"Other"**: 5%
- **Drugs**: 9%
- **Unknown**: 15%

Huang et al. J Allergy Clin Immunol 2011;129(1):162-8

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The poster children of anaphylaxis: IgE and the mast cell

First exposure to allergen

Second exposure to allergen

Mediators of Anaphylaxis

Castells, J Allergy Clin Immunol 2017
Mechanisms of Anaphylaxis

- Immunologic
  - IgE; Fc\(\varepsilon RI\)
  - Other: complement, IgG?
- Idiopathic
- Non-immunologic
  - Physical
  - Other:

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Clinical manifestations of anaphylaxis

<table>
<thead>
<tr>
<th>Signs/symptoms</th>
<th>Percentage of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td>&gt;90</td>
</tr>
<tr>
<td>-Urticaria and angioedema</td>
<td>85-90</td>
</tr>
<tr>
<td>-Flush</td>
<td>45-55</td>
</tr>
<tr>
<td>-Pruritus without rash</td>
<td>2-5</td>
</tr>
<tr>
<td>Respiratory</td>
<td>40-60</td>
</tr>
<tr>
<td>-Dyspnea, wheeze</td>
<td>45-50</td>
</tr>
<tr>
<td>-Upper airway angioedema</td>
<td>50-60</td>
</tr>
<tr>
<td>-Rhinitis</td>
<td>15-20</td>
</tr>
<tr>
<td>Dizziness, syncope, hypotension</td>
<td>30-35</td>
</tr>
<tr>
<td>Abdominal (n/v, diarrhea, cramping)</td>
<td>25-30</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1-8%</td>
</tr>
</tbody>
</table>

Lieberman P. In: Middleton et al 2014 1237-1259

Patterns of anaphylaxis

- Symptom onset is usually very quick, within minutes!
- Uniphasic
  - Symptoms resolve within hours of treatment
  - Most common presentation
- Biphasic
  - Symptoms resolve after treatment, but return several hours later
  - Onset of late phase varies between 1-72 hours of apparent resolution of initial phase
- Protracted
  - Symptoms do not resolve with treatment and may last >24 hours
Biphasic anaphylaxis

- In actuality, biphasic anaphylaxis is quite rare
- There are no reliable predictors of biphasic anaphylaxis, although patients who present with hypotension or with an unknown trigger may be more at risk
- Biphasic anaphylaxis is less likely in patients with food induced anaphylaxis

Lee et al. J Allergy Clin Immunol 2015;3:408-16

Monitoring biphasic anaphylaxis

- A 24 hour observation period is reasonable for:
  - Initial presentation of anaphylaxis with severe symptoms: hypotension, hypoxemia/respiratory failure
  - Need for repeated doses of epinephrine
  - Poorly controlled asthma
  - Prior history of biphasic anaphylaxis
Recall Case #2…

A 16 y/o male walks into the emergency room with urticaria and wheezing. insects. You diagnose anaphylaxis and investigate potential triggers. He had a steak sandwich for lunch about 5 hours ago, shortly after returning from his recent camping trip. He’s not sure about tick exposures. Otherwise, there are no other new food exposures, new medications, insect bites, or travel. He’s otherwise been in good health. What’s on the differential?

Delayed anaphylaxis

“Alpha Gal”

- IgE antibody directed against a mammalian oligosaccharide epitope, galactose-alpha-1,3-galactose (“alpha-gal”).
- The typical cycle:
  - Lone star tick (known carrier) bites human
  - Human makes IgE to the carbohydrate moiety (“sensitization”)
  - Human ingests mammalian meat (beef, pork, and lamb)
  - Human develops classic symptoms of anaphylaxis, only symptoms are typically delayed (3-6 hours after ingestion)
  - Patients with this condition will also react to the monoclonal antibody, cetuximab

Commins 2016. Allergol Int; 65(1): 16-20
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Differential Diagnosis

- Flush syndromes
- Vasodepressor (vasovagal syncope)
- Scombroid fish poisoning
- Other forms of shock
- Systemic mastocytosis or monoclonal mast cell activation syndrome
- Nonorganic disease (panic attack, etc.)
- Other
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**DIAGNOSTIC TOOLS**

-Can we routinely measure any these markers?

![Diagram of anaphylaxis mediators and diagnostic tools](Castells, J Allergy Clin Immunol 2017)
Establishing the Diagnosis of Anaphylaxis

- Serum tryptase
  - Commercial assays allow for detection of “total” and “mature”
  - More stable than histamine
  - Mature β-tryptase is stored in mast cell granules and released on activation
  - Increase above normal range of 11.4 ng/mL is indicative of acute mast cell/basophil activation; also consider levels of 2 ng/mL plus 1.2 times baseline significant increased

- Histamine
  - Can be obtained in both urine (24 hour measurement) and plasma
  - 24 hour collection is preferred since plasma histamine is only elevated for 30-60 minutes after the event
  - More sensitive that tryptase

Tryptase levels in children

- Children presenting to Montreal Children’s Hospital 2011-2015 with anaphylaxis
- Tryptase levels were evaluated when available within 2 hours of the reaction, and then re-evaluated after 9 months
- 203 children available
- Only 19% had elevated tryptase levels (defined as >11.4)
- Only risk factor for elevated tryptase level
  - Severe reaction
  - Food allergy due to milk trigger

De Shryver et al J Allergy Clin Immunol 2016;127:1138-42
Platelet activating factor (PAF)

- Serum PAF levels were directly correlated and serum PAF acetylhydrolase activity was inversely correlated with the severity of anaphylaxis
- Failure of PAF acetylhydrolase to inactivate PAF may contribute to the severity of anaphylaxis
- Further studies to assess the usefulness of PAF-AH as a biochemical marker
- Development of drugs to block the actions of PAF?

Vadas et al. NEJM 2008

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- Defining anaphylaxis
- Incidence and prevalence
- Some good news
- Causes of anaphylaxis
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- Differential diagnosis
- Fatal Anaphylaxis
- Diagnostic work-up
- **Acute treatment**
- Prevention of future episodes
Rapid progression of symptoms in anaphylaxis

- Median time to Respiratory or Cardiac Arrest
  - 30 minutes for foods
  - 15 minutes for venom
  - 5 minutes for iatrogenic reaction

Pumphrey RSH. Clin Exp Allergy 2000;30:1144-50

Actions of epinephrine

Simons FER. J Allergy Clin Immunol 2004;113:837-44
Epinephrine: Location, location

- IM vs SQ epinephrine

![Graph showing time to peak response for intramuscular and subcutaneous epinephrine]

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

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Antihistamines time of suppression

![Graph showing suppression time for different antihistamines]

Jones et al, Ann Allergy Asthma Immunol 2008. 100 (5) :452–56
Corticosteroids

- Median time to reach maximum serum concentration for oral hydrocortisone is approximately 1-2 hours after administration
- Rationale behind their use in anaphylaxis is extrapolated from their effectiveness in acute asthma
- There is no evidence from high quality, randomized controlled trials to confirm their effectiveness in the treatment of acute anaphylaxis
- Out of 22 studies that examined the association of corticosteroids with biphasic anaphylaxis, only 1 study seems to support their use


Immediate management of anaphylaxis

- ABC’s, vital signs, call for help
  - Supine position; pregnant patients should be on left side
  - Epinephrine 1:1000 (1mg/mL)
    - 0.01 mg/kg (up to 0.3mg) IM lateral thigh (child)
    - 0.2-0.5mg IM thigh (adult)
    - Repeat 5-15 minutes as needed
- Oxygen
  - Consider regardless of respiratory status
- Remember to remove inciting agent, if possible
After initial assessment

- Intravenous fluids
- Consider epinephrine infusion
- Consider antihistamines
- Consider corticosteroids
- Manage bronchospasm
- Consider vasopressors
- Consider glucagon, other agents
- ECG monitoring
- Hospitalization

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Some good news…

- Although anaphylaxis can be life threatening, the probability of dying is actually quite low

- The incidence of fatal anaphylaxis has not increased in line with hospital admissions for anaphylaxis

- Drugs are the most common reported cause of fatal anaphylaxis in several countries (including U.S.)
  - Estimated at 0.51 per million population in 2008-2010


<table>
<thead>
<tr>
<th>Fatal Anaphylaxis</th>
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<tbody>
<tr>
<td>Causes of Death</td>
</tr>
<tr>
<td>- 196 of 214 deaths determined</td>
</tr>
<tr>
<td>- Asphyxia – 96 people</td>
</tr>
<tr>
<td>- Shock – 88 people</td>
</tr>
<tr>
<td>- DIC – 7 people</td>
</tr>
<tr>
<td>- Epinephrine over-dose – 5 people</td>
</tr>
</tbody>
</table>

- Previous reactions do not predict future reactions
  - Over 2/3 of those dying from sting reactions and over 4/5 of those dying from drug anaphylaxis had no previous indication of their allergy
  - Those dying from food allergy had usually had previous reactions but these were typically not severe.

Pumphrey RSH. Anaphylaxis 2004;257:116-32
Risk factors for fatal anaphylaxis

- Adolescents
- Patients with a history of anaphylaxis
- Patients allergic to peanuts or tree nuts
- Patients with asthma
- Those presenting with the absence of cutaneous symptoms
- Delays in epinephrine administration

- Other: cardiovascular morbidity, upright posture, older age


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Preventing future episodes
Establishing the cause

- Establish the cause – contact your friendly allergist!
  - Skin and in vitro tests
  - Serum IgE to galactose-1,3-α-galactose
  - Baseline serum tryptase
  - Blood determination for 816V mutation
  - Bone marrow biopsy
  - Food and drug challenges

- Prevent it from happening again, if possible
  - Desensitizations, pre-medications

Lieberman et al. 2015. Ann Allergy Asthma Immunol 341-384

Prevention of future episodes

- Have patient wear and carry warning identification tags
- Teach self-injection of epinephrine
- Make the patient carry 2 epinephrine auto-injectors
- Teach patients about presence of hidden allergens
- Identify cross-reactive allergens in drugs
- Discontinue select medications, if possible
  - β-adrenergic blockers
  - Angiotensin-converting enzyme inhibitors
  - Angiotensin blockers
  - Monoamine oxidase inhibitors
  - Certain tricyclics
Food Allergy Fun

What about ORGANIC Peanut Butter?

It's a slightly more expensive risk of anaphylaxis.

www.foodallergyfun.com  TGF 2012