Anaphylaxis: Facts, Fallacies and the Fantastic

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Conflict of Interest
- Dr. Khan has no financial conflicts of interest to disclose relevant to this presentation.

Lecture Objectives
- Recognize the various clinical presentations of anaphylaxis
- Gain an understanding of the various etiologies of anaphylaxis
- Learn the appropriate management of anaphylaxis
History of Anaphylaxis

DECOUVERTE DE L’ANAPHYLAXIE
(The Discovery of Anaphylaxis)

Paul Portier on the Discovery of Anaphylaxis

- “We considered our work as almost finished when I proposed to Richet to proceed to some trials of immunization. My proposition did not arouse much enthusiasm in him and I considered it more or less as a routine completion of our work.
- It was then that we noticed with surprise that the results were not those we expected. No, the animals were not immunized. Certain ones seemed "sensitized".
- The fact appeared so unforeseen and paradoxical that Dr. Richet asked me if I had not mixed the animals in the two series: those vaccinated and the controls. I was almost sure not, but finally we began a new series to confirm the first result.”

Portier P. La Presse Médicale, 1952;60:679.

14 Jan 1902
- Dog Neptune received an injection of 0.05cc of toxin per kg. One hour after injection, the dog walked cheerfully about the laboratory.
- 17 Jan.
  - In order to see if the dog is sensitized, it was injected with 0.1cc of the toxin per kg.
- 18 Jan.
  - The dog did not appear ill, very cheerful.
- 10 Feb.
  - (26 days after first injection) the dog was in perfect health, cheerful, active, the coat was shiny. On this day at 2 PM, it was injected with 0.12cc toxin per kg. Immediately produced vomiting, defecation, trembling of front legs. The dog fell on the side, lost consciousness, and in one hour was dead.
“ANAPHYLAXIE”

When the phenomenon had been solidly established from the experimental standpoint, M. Richet decided to baptize it. I tried to persuade him of the inutility of creating a neologism, since there were already so many in the scientific literature, and especially as we have forgotten our Greek--- You might be right, answered Richet, if the phenomenon we have discovered is a rarity, but if it presents a certain general interest, we have to have a name for it--- At the moment he approached a small blackboard hidden under the stairs and asked me if I knew the Greek word for ‘immunity’, ‘protection’--- No, I said, I might have known it but I have forgotten--- It is “phylaxis”, and so let us affix a privative “a” --- The resulting word aphylaxie not being very euphonic, we decided to adopt the word anaphylaxie (anaphylaxis). At the moment we could not dream of the great value attached to this expression.”

Charles Richet Nobel acceptance speech 1913

“The discovery of anaphylaxis] is not at all the result of deep thinking, but of simple observation, almost accidental, so that I have had no other merit than that of not refusing to see the facts which presented themselves before me, completely evident.”

Updated Anaphylaxis Parameter

The diagnosis and management of anaphylaxis practice parameter: 2009 Update


http://www.jacionline.org/article/S0091-6749(10)01004-3/abstract

Outline

- Defining anaphylaxis
- Clinical features
- Causes of anaphylaxis
- Acute management of anaphylaxis
- Patient Education
- Key Summary Statements
What Is Anaphylaxis?

Summary Statement #6

Anaphylaxis is an acute, life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity that results from the sudden systemic release of mediators from mast cells and basophils. B

Definitions

- **ANAPHYLAXIS**
  - Clinical syndrome with multi-organ symptoms
    - cutaneous
    - respiratory
    - cardiovascular
    - gastrointestinal
  - IgE-mediated mechanism

- **ANAPHYLACTOID**
  - Identical symptoms as anaphylaxis
  - Non-IgE-mediated mechanism

3 Criteria for Diagnosis of Anaphylaxis

- **Anaphylaxis is likely when any 1 of 3 criteria are fulfilled**

  Criteria based on symptoms and separated based on:
  - acute onset of illness (regardless of allergen exposure)
  - after exposure to a likely allergen
  - after exposure to a known allergen

Definition of Anaphylaxis

(1) Acute onset of an illness (minutes to hours) with involvement of
   Skin/mucosal tissue (eg, hives, generalized itch/flush, swollen lips/tongue/uvula)
   AND
   Airway compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF)
   OR
   Reduced BP or associated symptoms (eg, collapse, syncope)


Definition of Anaphylaxis cont’d

(2) Two or more of the following after exposure to a likely allergen for that patient (minutes to hours)
   • Skin/mucosal tissue (eg, hives, generalized itch/flush, swollen lips/tongue/uvula)
   • Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF)
   • Reduced BP or associated symptoms (eg, hypotonia, syncope)
   • Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)


Definition of Anaphylaxis cont’d

(3) Hypotension after exposure to known allergen for that patient (minutes to hours)
   • Infants and children: low systolic BP (age-specific) or >30% drop in systolic BP
   • Adults: systolic BP <90 mm Hg or >30% drop from their baseline


Physiology of Anaphylaxis
Physiology of Life-Threatening Anaphylaxis

- Vasodilatation
  - Venous dilatation leads to venous pooling
    - causing a significant reduction in effective blood volume
- Capillary leak
  - reduction in absolute blood volume
- Bronchospasm and laryngeal edema
  - hypoxia

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Physiology of Anaphylactic Shock

- Compensatory initial tachycardia due to hypotension
- Bradycardia may occur later
  - May be confused with vagal reaction


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All that is Bradycardic may not be Vagal!

Clinical Features of Anaphylaxis
“SHOCK” ORGANS IN ANAPHYLAXIS

- Skin
- Respiratory tract
- Cardiovascular system
- Gastrointestinal tract

<table>
<thead>
<tr>
<th>Signs and Symptoms of Anaphylaxis</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td></td>
</tr>
<tr>
<td>Urticaria and angioedema</td>
<td>85-90</td>
</tr>
<tr>
<td>Flushing</td>
<td>45-55</td>
</tr>
<tr>
<td>Pruritus without rash</td>
<td>2-5</td>
</tr>
<tr>
<td>Respiratory</td>
<td></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>
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<tr>
<td>Abdominal</td>
<td></td>
</tr>
<tr>
<td>Nausea, vomiting, diarrhea, cramping pain</td>
<td>25-30</td>
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<tr>
<td>Miscellaneous</td>
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<td>Headache</td>
<td>5-8</td>
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<tr>
<td>Substernal pain</td>
<td>4-6</td>
</tr>
<tr>
<td>Seizure</td>
<td>1-2</td>
</tr>
</tbody>
</table>

Protracted Anaphylaxis

Initial Symptoms

Antigen Exposure

Possibly >24 hours

Time

Biphasic Anaphylaxis

- Incidence 1-20%
- Onset 1-78 hrs after initial event
- Most 2\textsuperscript{nd} events occur within 10 hrs
- Severity of 2\textsuperscript{nd} event variable
  - Rarely fatal
- Corticosteroids do not reliably prevent 2\textsuperscript{nd} anaphylaxis event

How Long To Observe After Anaphylaxis?

- 8-10 hr observation would cover most (not all reactions)
- Consider 24 hr observation for:
  - Oral administration of antigen
  - Hypotension or laryngeal edema
  - Onset of symptoms > 30 min after antigen
  - Requirement for high doses of epinephrine
- All patients discharged should have prescription and education for self-injectable epinephrine

Causes of Anaphylaxis
Anaphylaxis Case

- 2 yo boy had a history of urticaria, angioedema, wheezing, and occasionally cyanosis after ingestion of cow milk or milk containing products. Cow’s milk or egg white applied to the skin caused urticaria. Skin tests and RAST to milk and egg were positive.
- Another episode of anaphylaxis occurred after ingesting < 1 Tbsp of “pareve” labeled raspberry sorbet.


Anaphylaxis Case cont’d

- Raspberry Sorbet analysis
  - 10,956 U/ml milk allergen
- Subsequent investigation revealed that common equipment was used to package both pareve and dairy foods and the procedure to clean and flush equipment was inadequate to prevent carry over of milk
- kosher-pareve labeling may not provide complete assurance that a product is milk-free


Summary Statement #14 & 21

14. Food is the most common cause of anaphylaxis in the outpatient setting and food allergens account for 30% of fatal cases of anaphylaxis. (D)
21. Patients who experience anaphylaxis should be observed for longer periods if they have experienced food-induced anaphylaxis. (C)

Food Induced Anaphylaxis

- Many foods can cause anaphylaxis
- Almost all food anaphylaxis is from ingestion of food
- Certain foods more common causes
  - Children
    - Peanuts, tree nuts, milk, egg
  - Adults
    - Shellfish, peanuts, tree nuts, fish
    - Seeds (e.g. sesame seed) and spices (new onset adult food allergy)
Fatal Food Anaphylaxis

- Frequency: ~150 deaths/year
- Clinical features:
  - Biphasic reaction can contribute initially better, then recurs
  - Cutaneous symptoms may not be present
  - Respiratory symptoms prominent
- History: known food allergen
- Key foods: peanuts and tree nuts dominate (~90% of fatalities), fish, crustaceans
- Most events occurred away from home

Risk factors:
- Underlying asthma
- Delayed epinephrine
- Previous severe reaction
- Symptom denial
- Adolescents, young adults

Management of Food Anaphylaxis

- Proper identification of allergen
  - Skin testing
    - Low positive predictive value (frequent false positives)
  - Food challenge
- Education
  - Label reading, school notification, behavior modification
- Early use of self-injectable epinephrine
- Food immunotherapy
  - In clinical trials with oral and sublingual routes

Label reading used to be very challenging! Example: Cow's Milk

Contains cow's milk: Artificial butter flavor, butter, butter fat, buttermilk, casein, caseinates (sodium, calcium, etc.), cheese, cream, cottage cheese, curds, custard, Half&Half®, hydrolysates (casein, milk, whey), lactalbumin, lactose, milk (derivatives, protein, solids, melted, condensed, evaporated, dry, whole, low-fat, non-fat, skim), nougat, pudding, rennet casein, sour cream, sour cream solids, sour milk solids, whey (delactosed, demineralized, protein concentrate), yogurt. MAY contain milk: brown sugar flavoring, natural flavoring, chocolate, caramel flavoring, high protein flour, margarine, Simplesse®.

AS of January 1, 2006, all food containing “Big Eight Allergens” (cow’s milk, peanut, tree nut, hen’s egg, soy, wheat, fish, crustacean) in the U.S. MUST declare the ingredient on the label in COMMON language. Does NOT apply to non-Big 8 allergens (e.g., sesame).
## Anaphylaxis Case

- CW is a 14 yo WF with a history of large local reactions to “bees”. 3 weeks prior to evaluation she was stung in the forehead by a “bee” and within 5 minutes developed facial urticaria, chest tightness, and throat tightness which improved with H₁ & H₂ antagonists administered by her father a cardiologist.
- Skin testing to yellow jacket was positive

## Summary Statement #85 & 86

85. Anaphylaxis to insect stings has occurred in 3% of adults and 1% of children who have been stung, and can be fatal even on the first reaction. B
86. Cutaneous systemic reactions are most common in children, hypotensive shock is most common in adults, and respiratory manifestations occur equally in all age groups. B

## Sting Induced Anaphylaxis

- Common cause of anaphylaxis
- Hymenoptera
  - Yellow jacket - most common
  - Bees, hornets, wasps, fire ants (common in SE)
- Children with cutaneous-only reactions do not require immunotherapy
- Patients with other systemic reactions should be referred for testing and likely immunotherapy
- Venom immunotherapy reduces reaction rate from 40-60% to < 1-2%
  - Most patients can stop venom therapy after 5 yrs

## Drug-Induced Anaphylaxis

- Multiple drugs capable of causing anaphylaxis
- IgE mediated
  - Beta-lactam antibiotics, NSAIDs(?), chemotherapeutics, biologics, allergen immunotherapy, intraoperative agents, etc.
- Non-IgE mediated
  - Radiocontrast media, blood products, plasma expanders, opiates, omalizumab
Vaccine Anaphylaxis

- Rare
- 1 per million doses
- 150-350 cases of vaccine-anaphylaxis in U.S. annually
- IgE-mediated reactions more commonly due to vaccine components


MMR Vaccine & Egg Allergy

- Measles vaccine grown in chick-embryo fibroblasts
  - egg protein in vaccine: 0-1 ng ovalbumin/dose
  - Prospective study of 54 children allergic to eggs
    - 26 history of anaphylactic reactions to eggs
    - 22 positive DBPCFC to egg
  - All children had positive skin test to egg
  - 3/17 had positive skin tests to MMR vaccine
  - No child reacted to vaccination with MMR vaccine given as a single dose

Anaphylaxis to MMR Vaccine

- >55 cases reported
- Only 2 cases with history of egg allergy
  - not confirmed by skin test or challenge
  - 1 of these egg allergy history questionable
- Allergy to gelatin is major allergen
    - Confirmed IgE to gelatin in 1 patient with MMR anaphylaxis
    - skin test, RAST, RAST inhibition, immunoblot
    - 19 cases of MMR anaphylaxis
    - 18/19 had IgE to gelatin


Vaccines and Gelatin

- Vaccine-anaphylaxis to gelatin
  - MMR
  - Varicella
  - Japanese encephalitis

Anaphylaxis Case

- LB is a 17 yo WM who presented with recurrent syncopal episodes. These episodes were associated with pruritus, urticaria, lightheadedness, and syncope with urinary & fecal incontinence and occurred after playing basketball or ping-pong. However, he has performed more vigorous exercise without reactions. An echocardiogram, Holter monitor and head CT were all normal.
- Physical examination was unremarkable

Summary Statement #51

Exercise is the immediate trigger for the development of symptoms in exercise induced anaphylaxis (EIA). Typical symptoms include extreme fatigue, warmth, flushing, pruritus, and urticaria, occasionally progressing to angioedema, wheezing, upper airway obstruction, and collapse.

Exercise-Induced Anaphylaxis

- Reactions occur while exercising or shortly thereafter
- Premonitory symptoms
  - generalized warmth, pruritus
  - urticaria are usually 10-15 mm in diameter
  - angioedema of face, palms, and soles
- Food-dependent EIA
  - Usually related to a specific food ingested prior to exercise
  - shellfish, wheat, celery, tomato, and many others
- Predisposing factors
  - personal or family history of atopy
  - aspirin ingestion prior to exercise may trigger 30%
  - exercising in warm or humid weather

Summary Statement #55

All patients with exercise-induced anaphylaxis must be advised to stop exercising immediately at the first sign of symptoms because continued exertion causes the attacks to worsen. In addition, all patients should carry epinephrine auto injectors and exercise with a partner who can recognize symptoms and administer epinephrine if necessary.
Anaphylaxis Case

- MC is a 15 yo WF with a history of recurrent anaphylaxis since age of 5. Attacks consist of abdominal cramping, nausea, vomiting, diarrhea, flushing, pruritus and hypotension. Many of episodes will awaken her from sleep. Work up for gluten sensitive enteropathy, carcinoid, pheochromocytoma, and RAST to multiple foods was negative. Taking Benadryl 25 mg bid prevents attacks.

Summary Statement #58 & 59

58. The symptoms of idiopathic anaphylaxis are identical to those of episodes related to known causes. C

59. Patients with idiopathic anaphylaxis should receive an intensive evaluation, including a meticulous history to rule out a definite cause of the events. C

Idiopathic Anaphylaxis

- Diagnosis of exclusion
- Nocturnal anaphylaxis a clue
- More common in women
- Very rarely fatal
- Prognosis typically favorable with frequent remission

Overview of Anaphylactic Triggers
Treatment of Anaphylaxis

Summary Statement #7
The more rapidly anaphylaxis develops, the more likely the reaction is to be severe and potentially life-threatening.

Summary Statement #8
Prompt recognition of signs and symptoms of anaphylaxis is crucial. If there is any doubt, it is generally better to administer epinephrine.

Summary Statement #9-1
Epinephrine and oxygen are the most important therapeutic agents administered in anaphylaxis. Epinephrine is the drug of choice, and the appropriate dose should be administered promptly at the onset of apparent anaphylaxis.
Treatment of Anaphylaxis

= Epinephrine

Why Epinephrine is Best for Anaphylaxis

- Most rapid onset of action of any anti-allergic medicine
- Mechanisms of action
  - $\alpha$-agonist
    - increase BP by peripheral vasoconstriction
  - $\beta$-agonist
    - reverse bronchoconstriction
    - positive inotropic and chronotropic activity
    - increases cyclic AMP levels
    - inhibits further mediator release from mast cells and basophils

Treatment of Anaphylaxis

- Epinephrine
  - Drug of choice
  - Administer every 5-15 minutes as needed
- Pediatric Dosage
  - .01 mg/kg
- Adult Dosage
  - 0.2-0.5 ml (0.3-0.5 mg) of a 1:1,000 dilution

Dosing EpiPen in Children

Epipen: .3 mg epinephrine
Epipen Jr: .15 mg epinephrine

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<th>Age (yrs)</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>10</th>
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<tr>
<td>0.3 mg</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Dosing EpiPen in Children

TABLE III. Case study: For a child weighing 22.5 kg, which auto-injector is used—EpiPen Jr (0.15 mg) or EpiPen (0.3 mg)?

1. In a child weighing 22.5 kg, the average weight for a 7-year-old, the EpiPen Jr delivers a 1.5-fold overdose and the EpiPen delivers a 1.3-fold overdose.
2. The decision to use EpiPen Jr rather than EpiPen Jr may be guided by the presence of 1 or more of the following:
   - Concurrent diagnosis of asthma
   - Peanut, tree nut, milk, egg, fish or seafood anaphylaxis
   - Poor access to emergency medical services, eg, living or vacationing in a remote rural area
   - Dysfunctional/chaotic family situation
   - No reliable transportation available
3. History of previous life-threatening reaction (note, however, that absence of a history of a life-threatening reaction does not eliminate the possibility of such a reaction in the future.29,31,34)


Use of EpiPen in Children with Anaphylaxis Reduces Hospitalization

- Retrospective survey of children with anaphylaxis who attended an allergy clinic in North Adelaide Australia
- 45 episodes of anaphylaxis
  - EpiPen given 2 (14%)
  - EpiPen not given 32 (71%)
- Hospitalization for anaphylaxis
  - EpiPen given 2 (14%) p < .05
  - EpiPen not given 15 (47%)


How Often to Administer Epinephrine?

- Epinephrine may be administered every 5 to 10 minutes as necessary
- If the clinician deems it appropriate, the 5 minute interval between injections can be liberalized to promote more frequent administration
- Epinephrine should be administered as soon as the diagnosis of anaphylaxis is suspected


When to Administer Epinephrine?

- Although the diagnosis of anaphylaxis usually depends on involvement of two organ systems (e.g., skin plus respiratory, skin plus cardiovascular), anaphylaxis may present as an acute cardiac or respiratory event or with hypotension as the only manifestation of anaphylaxis.
- In the case of suspected anaphylaxis even if it involves only one system, such as the skin, epinephrine administration may be indicated.

Body Position in Anaphylaxis

- Patients with anaphylactic shock should be kept lying down
- Legs should be raised to shunt effective circulation to head, heart and kidneys
- Patients who are already supine should use their epinephrine while supine
- Keep patients supine until asymptomatic
- Fatal cases associated with posture changes

Summary Statement #9-2
The consensus of experts is that, in general, treatment in order of importance is: epinephrine, patient position, oxygen, intravenous fluids, nebulized therapy, vasopressors, antihistamines, corticosteroids, and other agents.

Additional Measures in Anaphylaxis

- Oxygen
  - Pulse oximeters very useful to have in shot room
- Intravenous access
  - IV fluids if hypotensive
  - IV epinephrine if IM not effective
- Body position

Summary Statement #10
Appropriate volume replacement either with colloid or crystalloids and rapid transport to the hospital is essential for patients who are unstable or refractory to initial therapy for anaphylaxis in the office setting.
Secondary Anaphylaxis Therapy

- Do not delay the administration of epinephrine, oxygen or volume expanders by the preparation and administration of the following
  - Albuterol
  - Antihistamines
  - Systemic steroids
    - **No role for acute anaphylaxis**
  - H2-blockers
  - Glucagon
    - for beta-blocker-induced anaphylaxis
  - Atropine

Patient Education

Summary Statement #100

Patient education might be the most important preventive strategy. Education can emphasize hidden allergens, cross-reactivity between various allergens and drugs, unforeseen risks during medical procedures, and when and how to use self-administered epinephrine. Physicians should educate patients about the risks of future anaphylaxis, as well as the benefits of avoidance measures.

Epinephrine Often Delayed or Not Given in Fatal Anaphylaxis

<table>
<thead>
<tr>
<th></th>
<th>Minutes to Arrest</th>
<th>First Adrenaline</th>
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<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
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<tr>
<td>Iatrogenic (55)</td>
<td>5</td>
<td>1-80</td>
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<tr>
<td>Food (37)</td>
<td>30</td>
<td>6-360</td>
</tr>
<tr>
<td>Venom (32)</td>
<td>15</td>
<td>4-120</td>
</tr>
</tbody>
</table>

Only 14% of fatal anaphylaxis patients received epinephrine prior to cardiorespiratory arrest

Most Patients and Physicians Do Not Know how to use Self-injectable Epinephrine

- Most patients (68%) and physicians (79%) do not know how to use self-injectable epinephrine
- Many anaphylactic patients do not carry self-injectable epinephrine


Conclusions

- Clinical features of anaphylaxis vary and do not always include hypotension
- Epinephrine is the treatment of choice and should be administered as soon as possible
- Patients require education on when and how to administer epinephrine as well as allergen avoidance