The Many Faces of Anaphylaxis

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What the everyone pictures when they think of anaphylaxis...

https://youtu.be/SdDPoFcBZEY

Objectives

• Discuss various cases and different causes of anaphylaxis
• Review pathophysiology of immediate type hypersensitivity reactions
• Review diagnosis and management of anaphylaxis
• Review mast cell activation disorders
• Provide updates on potential treatments and prevention measures
Question 1

• Appropriate 1st-line therapy for the treatment of anaphylaxis includes the following:

  a) Epinephrine
  b) H1 antihistamines
  c) H2 antihistamines
  d) Glucocorticoids
  e) IVF
  f) All of the above

Question 2

• Based on current guidelines, glucocorticoids and antihistamines SHOULD be used in the following situations:

  a) To prevent biphasic anaphylactic reactions
  b) To prevent anaphylaxis related to certain chemotherapeutic protocols
  c) To prevent anaphylaxis to iso-osmolar, non-ionic radiopaque contrast media agents
  d) To prevent anaphylaxis during rush immunotherapy protocols
  e) All of the above
  f) A and C only
  g) B and D only

Question 3

• The following factors have been associated with an increased risk of biphasic anaphylactic reactions:

  a) Anaphylaxis caused by any drug in patients <18
  b) Anaphylaxis caused by an unknown trigger
  c) Anaphylaxis with cutaneous manifestations
  d) Anaphylaxis with wide pulse pressures
  e) Anaphylaxis with severe initial symptoms
  f) Anaphylaxis treated with steroids in patients <18
  g) Anaphylaxis requiring more than one dose of epinephrine
  h) All of the above
Question 4

Based on current guidelines, all patients with anaphylaxis should be observed for an extended period of time in the ER (i.e. >6 hours)?

a) True
b) False

Case 1

A 2 year old female with no prior medical history developed progressive symptoms of coughing, nausea, vomiting and hives over 20 minutes after eating pistachio ice cream.

- Mother treated with cetirizine and called 911.
- EMS administered epinephrine and Benadryl – transferred to ER.

In the ER, patient had persistent symptoms of hives and hypotension.

- Treated with additional epinephrine, Benadryl, corticosteroids and IVF. Symptoms resolved.
- Admitted for observation overnight with no recurrence.
- Follow-up allergy evaluation confirmed allergy to pistachio and cashew with large SPTs (>20mm wheals). All other nuts were negative.
Anaphylaxis

• Initially defined in 1901 by Charles Richet and Paul Portier as the “absence” (ana) of “protection” (phylaxis).
• It is an acute life threatening, systemic allergic reaction associated with different mechanisms, triggers, clinical presentation and severity.
• Because of this variability, diagnosis can be missed in 80% of patients seen in ED, undergoing surgery and anesthesia, or being treated with chemotherapy, mAbs or other biologic agents.

Anaphylaxis

• NIAID and FAAN workgroup definition (2006) with anaphylaxis likely if one of the 3 criteria met:
  – Acute onset of an illness with involvement of the skin mucosal tissue, or both with either respiratory compromise or reduced blood pressure / associated symptoms of end-organ dysfunction
  – Two or more of the following occurring rapidly after exposure to a likely allergen
    • Involvement of skin-mucosal tissue
    • Respiratory compromise
    • Reduced blood pressure or associated symptoms
    • Persistent gastrointestinal symptoms
  – Reduced blood pressure as a result of exposure to a known allergen trigger

• Sensitivity 95%
• Specificity 71%
• Meeting diagnostic criteria is not prerequisite for epinephrine use especially in context of exposure to known allergen (i.e AIT)
Anaphylaxis

• Lifetime prevalence estimated to be 1.6 – 5.1%
• Fatal anaphylaxis is rare with prevalence rates between 0.47 to 0.69 million persons (0.25% - 0.33% of anaphylactic events)
  – Drugs (29-58%), stings (3.3-54%), foods (2-6.7%)
• Estimates of biphasic anaphylaxis varies from <1% to 20% of patients
  – More severe initial presentation (OR 2.11)
  – Repeated epinephrine doses required (OR 4.82)

Anaphylaxis

• Risk factors for severe anaphylaxis
  – Cardiovascular disease
  – Asthma
  – African-American race
  – Older age
  – Male sex (though anaphylaxis is more common in females)
  – Additional coexisting co-morbid conditions
• Medications are the leading cause in adults
  – Antibiotics, NSAIDs, biologics and immunomodulators
• Foods and insect stings are most common in children
• Many cases are idiopathic

Food-induced Anaphylaxis

• Leading cause of ED visits for anaphylaxis with estimated 30,000 cases per year
• Estimated to effect 8% of children and 11% of adults in the US
• Rates increased by 50% between 1997-2011 in US children
• Annual direct medical costs of $225 million
  – Office (52.5%), ED (20%), inpatient (11.2%), Epi (8.7%)
• 30-86% of patients have epinephrine available
Drug-induced Anaphylaxis

- ADRs effect 1/10th of world's population and 20% of hospitalized patients
  - Over 10% of all ADRs are DHRs
  - 8% of patients self report drug allergy, and 11% of those are reported anaphylactic reactions
  - Drugs may be responsible for up to 20% of fatalities due to anaphylaxis
  - Antibiotics (β-lactams); chemotherapy agents (platins and taxanes); chimeric, humanized and human mAbs; general anesthetics; immunotherapy allergens
  - Drugs may cause 20% of fatalities due to anaphylaxis

Insect venom-induced Anaphylaxis

- Reaction types include large local (LL) or systemic allergic reactions (SAR)
  - LL reactions occur in an estimated 5% of adults
  - SARs occur in 2.3% of adults and 1% of children
- Some studies indicate 23% of anaphylaxis due to insect stings
- Fatal anaphylaxis due to insect sting estimated at 40 cases per year in the US.
- High frequency of asymptomatic sensitization with >20% of adults with detectable venom sIgE
- Not familial and not associated with atopy

Case 2

- 65 yo male with history of prostate cancer presents for evaluation of possible local anesthetic allergy
- He reports prior reaction to local anesthetic injection given during treatment for prostate cancer several years ago
- Reported sudden onset of flushing, itching and rapid heart rate after injection
Case 2

- He has been avoiding local anesthetics since but now has pending dental surgery
- Has noted similar mild symptoms following vaccines with flushing and itching reported
- Most recently had severe symptoms of flushing, itching and lethargy after taking bowel preparation for screening colonoscopy
- Treated with Benadryl with gradual improvement

Case 2

- Testing for local anesthetic allergy was negative
- Discussed possibility of allergy polyethylene glycol based on history
- Offered additional allergy testing and challenge but patient declined
- Preferred continued avoidance of PEG containing products and carry epinephrine

PEG / Macrogol Allergy

- Widely used additive in pharmaceuticals, cosmetics and foods (PEGs, macrogols, polysorbates)
- Different types exist depending on molecular weight
- Rare cause of anaphylaxis
- May be suspected in recurrent reactions to seemingly unrelated compounds / products
- Thought to be IgE mediated based on reports of reactions with + SPT and IDTs. May also have alternate non-IgE mediated mechanisms including complement
- Treatment focused on avoidance and therapeutic measures as needed.
Anaphylaxis Phenotypes and Endotypes

- Phenotypes
  - Type-I hypersensitivity like reactions
  - Cytokine storm-like reactions
  - Mixed reactions
- Endotypes
  - IgE mediated mechanisms
  - Non-IgE mediated mechanisms
  - Cytokine release
  - Mixed reactions
  - Direct activation of immune cells

IgE-mediated Anaphylaxis

- Characterized by classic symptoms of mediator release from mast cells and basophils
  - Cutaneous - flushing, pruritus, hives, angioedema
  - Respiratory - shortness of breath, wheezing, O2 desaturation
  - Gastrointestinal – vomiting, diarrhea
  - Cardiovascular – hypotension, cardiovascular collapse

IgE-mediated Anaphylaxis

- Antigen mediated cross linking of IgE bound to high-affinity receptor FcεRI on blood basophils and tissue mast cells inducing mediator release
  - Preformed mediators – histamine, proteases (tryptase)
  - De novo synthesis of inflammatory mediators – leukotrienes (LTs), prostaglandins (PGs), and cytokines
- Reaction abrogated in mouse models lacking FcεRI and mast cells
- Anti-IgE mAb omalizumab can reduce the risk of severe allergic reactions in food and venom allergy
- IgE levels do not indicate absolute clinical activity
Non-IgE-mediated Anaphylaxis
- Atypical symptoms including chills, fever, generalized malaise
- May be followed by hypotension, desaturation and cardiovascular collapse
- Mechanisms may include
  - IgG-mediated anaphylaxis
  - Complement mediated anaphylaxis
  - Cytokine storm due to proinflammatory mediators such as TNF-α, IL-1β and IL-6
  - G-coupled receptor MRGPRX2 induced anaphylaxis

Non-IgE-mediated Anaphylaxis
- IgG can induce passive systemic anaphylaxis (PSA) reactions in mouse models
  - Requires much large dose of antigen
  - Required systemic absorption of ingested antigen
- IgG1, IgG2a, IgG2b can induce PSA
- IgG-PSA reduced in FcγRIII-/- and enhanced in FcγRIIB-/- mice
- Mice deficient in IgG2 and FcγRIII are protected in several ASA models
Non-IgE-mediated Anaphylaxis

- Complement mediators of anaphylaxis
  - C3a, C4a, C5a anaphylatoxins are potent mediators
  - Elevated levels noted in human anaphylaxis and correlate with severity of the reaction
  - Injection of low dose induced W/F reactions
  - Reduced reactions in deficient mice
  - Often acts synergistically with IgE-mediated reactions

Non-IgE-mediated Anaphylaxis

- Cytokine storm-like reactions
  - Release of proinflammatory mediators such as TNF-α, IL1β and IL6 from immune cells
  - Triggers include mAbs and chemotherapy agents
  - Characterized by chills, fever, generalized malaise, and followed by hypotension
  - Premedication with COX1 inhibitors and corticosteroids may reduce intensity of reactions
Non-IgE-mediated Anaphylaxis

- G-coupled receptor MRGPRX2
  - Expressed on mast cells and other immune cells
  - Activated by drugs with tetrahydroisoquinoline (THIQ) motifs
    - quinolone antibiotics (ciprofloxacin and levofloxacin)
    - general anesthetics (rocuronium and atracuronium)
    - Icatibant
  - Activation results in non-IgE-mediated mediator release
  - Only proven in mouse models

![Pathway of Anaphylaxis](image)

<table>
<thead>
<tr>
<th>Trigger</th>
<th>Environmental Allergens</th>
<th>Food and Allergens</th>
<th>Antibodies</th>
<th>Chemicals</th>
<th>Other Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Degranulation</td>
<td>Mast cell release</td>
<td>Histamine</td>
<td>Prostaglandins</td>
<td>Histamine</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Rash, itching, urticaria</td>
<td>Swelling, angioedema</td>
<td>Shortness of breath</td>
<td>Swelling, angioedema</td>
<td>Shortness of breath</td>
</tr>
<tr>
<td>Treatment</td>
<td>Epinephrine</td>
<td>Antihistamines</td>
<td>Steroids</td>
<td>Antihistamines</td>
<td>Steroids</td>
</tr>
</tbody>
</table>

**TABLE 1:** Etiologic mechanisms of anaphylaxis and their distinguishing characteristics

<table>
<thead>
<tr>
<th>Type</th>
<th>Food</th>
<th>Insect sting</th>
<th>Drug</th>
<th>Insect sting</th>
<th>Other Drugs</th>
<th>Other Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ig-mediated</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Allergic</td>
<td>IgE</td>
<td>IgE</td>
<td>IgE</td>
<td>IgE</td>
<td>IgE</td>
<td>IgE</td>
</tr>
</tbody>
</table>

**References:**
- Cassells MJ, et al. JACI 2017

*Abbreviations: IgE, Immunoglobulin E; IgG, Immunoglobulin G.*
Case 3

- 19 yo female with recent episodes of lightheadedness and near syncope during training runs at college
- Had hives on one occasion
- Symptoms do not occur every time she trains
- Treated with Benadryl with improvement
- Prescribed epinephrine

Additional history suggests symptoms only occur after patient has eaten prior to training
- Has occurred with bagel ingestion and other wheat containing foods
- Seems to tolerate fruits and energy bars
- No history of food allergy or reactions without exercise
- Skin testing shows equivocal reaction to wheat and a few pollen allergies including grass
- sIgE wheat 0.42, total IgE 205
- Daily cetirizine and elimination of wheat ingestion 4 hours prior to exercise prevented recurrence
Food-dependent Exercise Induced Anaphylaxis (FDEIA)

- Recognized for over 30 years but FDEIA is frequently misdiagnosed and pathophysiology remains unclear
- Any food may trigger but wheat (omega-5 gliadin) is the dominant cause.
  - Component analysis of specific epitopes may be of use
- Other cofactors include NSAIDs, alcohol, and menstrual period
- FDEIA diagnosis is based on a combination of provocation tests
  - Food challenge
  - Cofactor challenge
  - Combined food–cofactor challenge or a challenge with high amounts of the culprit food.

Food-dependent Exercise Induced Anaphylaxis (FDEIA)

- Provocation tests mimicking real life environment improve diagnosis
- Management is based on avoidance of the culprit food and the cofactors
- Monoclonal antibodies (omalizumab) and food immunotherapy may have a role in future management

Anaphylaxis Diagnosis

- As with everything, most important is history
  - Possible triggers
  - Clinical symptoms
- Is there available testing to confirm the diagnosis?
  - SPT / IDT to possible antigens
  - Serology and sIgE testing
  - Tryptase and other mediators
    - 24-hour urine studies for N-methylhistamine, PGD₂ and 9α,11β-PGF₂α, LTE₄ and LTC₄ where available
    - Basophil activation test
    - cKit D816V mutation analysis in cases of MCAD
Case 4

- 75 yo female with long history of flushing, lightheadedness, weakness, and fatigue.
- Seems to becoming more prevalent. Feels unable to drive anymore due to symptoms.

Case 4

- She has been on multiple medications including drugs for her Type 2 DM and HTN
- Meds have been adjusted and reduced without improvement.
- She has noted increased symptoms with NSAID use
- She denies any specific allergic trigger or exposure. No food or environmental allergies.
Case 4

- Baseline serum tryptase is 18 ng/ml
- Bone marrow biopsy showed normal cellularity and clonality.
- cKit D816V mutation +
- Treated with high dose antihistamines and montelukast with improvement.
- Serial tryptase levels remain elevated but no progression of symptoms on treatment.

Mast Cell Activation Disorders (MCAD)

- Constellation of disorders resulting from either an abnormal baseline production of mast cell mediators or abnormal and excessive mast cell response to perceived trigger.
- Criteria for MCAS
  - Episodic multisystem symptoms consistent with mast cell activation
  - Appropriate response to medications targeting mast cell activation
  - Documented increase in validated markers of mast cell activation systemically (serum or urine) during symptomatic period compared with patients baseline.
Mast Cell Activation Disorders (MCAD)

- Present with symptoms of mast cell activation
  - Recurrent hypotension and cardiovascular collapse
  - Cutaneous flushing, tachycardia, gastrointestinal cramping, nausea, vomiting, diarrhea
  - Chronic urticaria and angioedema rarely present
  - More prone to hymenoptera venom allergy (HVA)
- Elevated tryptase or other biomarkers at baseline or following symptomatic event
- May have + cKIT D816V mutation

**TABLE V. Diagnostic criteria for systemic mastocytosis**

<table>
<thead>
<tr>
<th>Major and at least 1 minor criterion or 3 minor criteria are required for diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major: Multifocal aggregates of ≥15 mast cells in a noncutaneous tissue biopsy specimen</td>
</tr>
<tr>
<td>Minor: Aberrant mast cell morphology (e.g., spindle-shaped, hypogranulated, aberrant nucleus)</td>
</tr>
<tr>
<td>Aberrant CD25 and/or CD2 expression on mast cells</td>
</tr>
<tr>
<td>Presence of a codon 816 KIT mutation in blood or lesional tissue</td>
</tr>
<tr>
<td>Serum baseline tryptase level &gt;20 ng/mL (not valid if the patient has another hematologic neoplasm)</td>
</tr>
</tbody>
</table>

*Markers of mast cell clonality.

Akin C. JACI 2017

Molderings G. Naunyn-Schmiedeberg's Arch Pharmacol 2016

Mast Cell Activation Disorders (MCAD)

- Treatment strategies:
  - avoidance of triggers
  - pharmacologic management of mast cell mediators
  - treatment of associated disorders
  - cytoreductive treatment for clonal disease

*Fig. 8* Low therapy is not sufficiently effective at remission doses, add...
Treatment of Anaphylaxis

• Epinephrine is the ONLY 1st-line treatment
  – Non-selective agonist of all adrenergic receptors
  – Treats and prevents escalation of symptoms
• Maximal efficacy within 10 min of IM injection
to lateral thigh (preferred location)
• Preferred treatment for uniphasic and
biphasic reactions
• Delayed administration may result in higher
morbidity and mortality

Treatment of Anaphylaxis

• Antihistamines
  – Four antihistamine receptors – H1, H2, H3, H4
  – H1 most relevant during treatment of anaphylaxis
  – Onset 30 min after oral administration but peak
concentration may take 60-120 minutes
  – Beneficial for treating cutaneous symptoms
    • Urticaria, flushing, pruritus
    • Lack vasoconstrictive, brochodilatory, ionotropic and mast
cell stabilizing benefits of epinephrine
Treatment of Anaphylaxis

• Corticosteroids
  – No proven role or efficacy in acute management
  – Slow onset of action through binding to receptor, translocation to nucleus, inhibition of gene expression and production of new cytokines
  – May not show results or benefits for 4-6 hours
  – May reduce length of hospital stay but do not prevent recurrent ER visits

Treatment of Anaphylaxis

• Based on very low quality of evidence the updated guidelines suggest the following specific recommendations regarding use of antihistamines and corticosteroids:
  – Recommend against routine use to prevent biphasic reactions and anaphylaxis to iso-osmolar, non-ionic RCM
  – Recommend for routine use to prevent anaphylactic reaction to certain chemotherapeutic agents and during rush immunotherapy protocols

Treatment of Anaphylaxis

• Need for prolonged observation
  – Meta analysis showed NPVs for biphasic reactions
    • NPV for 1-hour observation was 95%
    • NPV for 6-hour observation was 97.3%
  – Limited incremental benefit for prolonged observation except for high risk anaphylactic patients or patients at high risk for biphasic reactions
  – Prolonged observation cost effective for patients at high risk of anaphylaxis
  – Patient with non-severe anaphylaxis and prompt response to single dose of epinephrine – 1 hour observation may be appropriate
Treatment of Anaphylaxis

- Desensitization
  - Enhanced safety and efficacy over last 15 years
    - Protocols for chemotherapy, mAbs, and antibiotics
    - Inhibitory mechanisms induced at low antigen doses which dominate and prevent anaphylaxis
  - Largest desensitization study to date
    - 370 patients received 2177 desensitizations to 15 drugs
    - 93% had no or mild reactions
    - 7% had moderate to severe reactions
    - No deaths
    - All completed desensitization and subsequent treatment

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Anaphylaxis - 2019 practice parameter update

Extended Observation to Detect Biphasic Anaphylaxis: Number Needed to Treat

![Graph showing number needed to treat with severe initial anaphylaxis symptoms and multiple epinephrine doses.]

- Severe initial anaphylaxis symptoms
  - Biphasic OR 4.52 (95% CI 1.37 – 8.5)
  - NNT = 50(17 – 88)

- Multiple epinephrine doses
  - Biphasic OR 4.80 (95% CI 1.32 – 10.3)
  - NNT = 50(17 – 27)

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Acute Treatment

- Systemic Hives:
  - Respiratory symptoms w/o Hypotension
- Anti-Histamines
- Consider Epinephrine

- Acute Onset of:
  - Hypotension
  - Laryngeal Edema
  - O2 Desaturations
  - Seizures

- Epinephrine IM REPEAT: q 5 min x 3
  1. Anti-Histamines H1 + H2
  2. IV Fluids
  3. Oxygen
  4. Corticosteroids
  5. Glucagon (if applicable)
  6. Consider Body Fluids Inhibitor (if ACE)

- Prophylaxis
  - Immunotherapy: Environmental, Food, Hymenoptera
  - Anti-IgE
  - Pymatase kinase inhibitor (Clowel Westcrf/K屎eier)
  - Desensitization

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Cassells M JACI 2017
BTK Inhibitors to prevent Anaphylaxis

- BTK is located downstream of FcεRI and is essential to FcεRI activation of mast cells
- BTK deficient mice have impaired anaphylaxis
- BTK important in B-cell maturation and BTK deficiency results in XLA
- Currently BTK inhibitors approved to treat B-cell leukemia and lymphomas
- Studies looking at use for allergic disorders
Short-term ibrutinib therapy suppresses skin test responses and eliminates IgE-mediated basophil activation in adults with peanut or tree nut allergy

Thirteen is the charm in anaphylaxis

- Gowthaman et al. discovered a subset of T follicular helper cells (TFH13) that direct B cells to generate high-affinity IgE.
- TFH13 cells are induced by allergens but not during parasite infection.
- Transgenic mice lacking these cells show impaired production of high-affinity, anaphylactic IgE.
- TFH13 cells, which are elevated in patients with food and aeroallergies, may be targeted in future antianaphylaxis therapies.
**Question 1**

• Appropriate 1<sup>st</sup>-line therapy for the treatment of anaphylaxis includes the following:

  a) Epinephrine
  b) H<sub>1</sub> antihistamines
  c) H<sub>2</sub> antihistamines
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  e) IVF
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**Question 2**

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Question 4

Based on current guidelines, all patients with anaphylaxis should be observed for an extended period of time in the ER?

a) True
b) False
References

- Anaphylaxis - 2019 practice parameter update
- Castells M. Diagnosis and management of anaphylaxis in precision medicine. J Allergy Clin Immunol 2017; 140:321-33
- Stone C, et al. Immediate hypersensitivity to polyethylene glycols and polysorbates: more common than we have recognized. J Allergy Clin Immunol 2016; 137:1674-1680