The Many Faces of Anaphylaxis

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

https://youtu.be/SdDPoFcBZcY
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
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
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.
Case 1

• 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
Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

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

AND AT LEAST ONE OF THE FOLLOWING:

- Sudden respiratory symptoms and signs (e.g., shortness of breath, wheeze, cough, stridor, hypoxemia)
- Sudden reduced BP or symptoms of end-organ dysfunction (e.g., hypotonia [collapse], incontinence)

OR 2. Two or more of the following that occur suddenly after exposure to a likely allergen or other trigger* for that patient (minutes to several hours):

- Sudden skin or mucosal symptoms and signs (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
- Sudden respiratory symptoms and signs (e.g., shortness of breath, wheeze, cough, stridor, hypoxemia)
- Sudden reduced BP or symptoms of end-organ dysfunction (e.g., hypotonia [collapse], incontinence)
- Sudden gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

OR 3. Reduced blood pressure (BP) after exposure to a known allergen** for that patient (minutes to several hours):

- Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP***
- Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

* For example, immunologic but IgE-independent, or non-immunologic (direct mast cell activation)
** For example, after an insect sting, reduced blood pressure might be the only manifestation of anaphylaxis; or, after allergen immunotherapy, generalized hives might be the only initial manifestation of anaphylaxis.
*** 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 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years. Normal heart rate ranges from 80-140 beats/minute at age 1-2 years; from 80-120 beats/minute at age 3 years; and from 70-115 beats/minute after age 3 years. In infants and children, respiratory compromise is more likely than hypotension or shock, and shock is more likely to manifest initially by tachycardia than by hypotension.

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

WAO Anaphylaxis Guidelines 2011
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 word’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 (B-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 Anaphyaxis

• Antigen mediated cross linking of IgE bound to high-affinity receptor $F_{c\varepsilon}RI$ 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 $F_{c\varepsilon}RI$ 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 IgG₁ and FcγRIII are protected in several ASA models
At low concentration of IgG Abs

Ab isotypes and FcRs

Antigen

IgE

FcεRI

Mast cells

Effector cells

At high concentration of antigen/IgG Abs

IgG Activating FcγR

Neutrophils

Monocytes/macrophages

Potential mediators

Histamine
CysLTs
Prostaglandins
Heparin
Proteases
Serotonin

Histamine
PAF
CysLTs

PAF
CysLTs

Various cytokines/chemokines

Reber L, et al. JACI 2017
CONDITIONS:
Low or High Ag; Low Ab

RESULT: IgE-Dependent Anaphylaxis

CONDITIONS:
High Ag + Ab, Ab>Ag

RESULT: IgG-Dependent Anaphylaxis

RESULT: No Anaphylaxis

RESULT: IgE + IgG-Dependent Anaphylaxis

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 atracurium)
    • Icatibant
  – Activation results in non-IgE-mediated mediator release
  – Only proven in mouse models
Pathways of Anaphylaxis

Triggers
- Environmental Allergens
  - Food Allergens
  - Antibiotics
  - Chemotherapy Monoclonal Antibodies
  - Other Drugs
  - Hymenoptera Venom
- Chemotherapy
  - Monoclonal Antibodies
- Contrast Dyes
  - Oversulfated chondroitin sulfate
  - Glycosaminoglycans
  - Dyalisis Membranes

Phenotype
- Type I IgE/non-IgE
- Cytokine-release
- Mixed
- Complement

Endotypes
- Mast Cell
- Basophil
- T-Cell Macrophage Monocyte
- Basophile
- Mast Cell

Biomarkers
- Histamine
- Tryptase
- TNF-α
- IL-6
- IL-1β
- c5a
- c4a

Symptoms
- Flush, Pruritis, Urticaria, Throat Tightness
- Shortness of Breath, Back Pain, Nausea, Vomiting, Diarrhea, Cardiovascular Collapse
- Fever, Chills/Rigors, Nausea, Pain, Headache
- Hypotension, Oxygen desaturation
- Fever, Chills/Rigors, Nausea, Pain, Headache, Flushing, Pruritis, Rash, Urticaria, Throat Tightness, Shortness of Breath, Nausea, Vomiting, Diarrhea, Cardiovascular Collapse

Treatment
- Epinephrine

Desensitization
- Yes
- Selected Cases
- Selected Cases
- No

Cassells M JACI 2017
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*Mechanisms differ for different agents.
**Biomarkers:**

- **Skin Test Tryptase**

**Mediators of Anaphylaxis**

- **Histamine** → Skin + Blood vessels
- **PGD$_2$** → Brain + Flushing
  - Vasodilation
- **Tryptase** → Fibrinogen $\alpha$ chain
  - C3a + C5a
- **Bradykinin** → Hypotension + Swelling
- **Leukotrienes** → Bronchospasm + Swelling
- **PAF** → Vasodilation

*Image Source: Cassells M JACI 2017*
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
Case 3

- 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 9-α-11-β PGF₂, LTE₄ and LTC₄ where available
  – Basophil activation test
  – cKit D816V mutation analysis in cases of MCAD
Anaphylaxis Diagnosis

Initial Triggers:
- Food
- Drug
- Hymenoptera
- Exercise
- Environmental
- Unprovoked

Sudden Onset of Symptoms in 2 or More Organs or Hypotension, Laryngeal Edema, Cardiovascular Collapse

Tryptase
- Elevated
  - 30-60 min of Symptoms
  - Normal levels >11.4 ng/ml
- Normal
  - 4-6 wks after event

Baseline Tryptase
- Elevated
- KIT D816V Mutation
  - +/- Skin Mastocytosis
  - Recurrent Hypotension
- Normal

Skin Testing
- Specific IgE
  - Basophil Activation Test (Research Use)
- +
  - Environments
  - Drugs
  - Foods
  - Hymenoptera
- -

Bone Marrow Biopsy
- +
  - +
  - Mast Cell Activation Syndrome (MCAS), Cutaneous Mastocytosis
  - Mast Cell Activation Disorder (MCAD)
  - Systemic Mastocytosis, Monoclonal Mast Cell Activation Disorder (MMCAD)
  - Allergen Specific Anaphylaxis, Food Triggered Exercise Induced Anaphylaxis (FTEIA)
  - Idiopathic Anaphylaxis (IA), Exercise Induced Anaphylaxis (EIA)
- -
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**

Major and at least 1 minor criterion or 3 minor criteria are required for diagnosis

**Major:** Multifocal aggregates of $\geq 15$ mast cells in a noncutaneous tissue biopsy specimen

**Minor**

- Aberrant mast cell morphology (e.g., spindle-shaped, hypogranulated, aberrant nucleus)
- Aberrant CD25 and/or CD2 expression on mast cells*
- Presence of a codon 816 \textit{KIT} mutation in blood or lesional tissue*
- Serum baseline tryptase level $>20 \text{ ng/mL}$ (not valid if the patient has another hematologic neoplasm)

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*Markers of mast cell clonality.*
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

If 1st line therapy is not sufficiently effective even at maximum doses, add:

2nd line: Immuno-suppressive drugs

3rd line: Omalizumab

4th line: Inhibitors of tyrosine kinases and other kinases

5th line: Investigational drugs

last choice: Cytoreductive drugs, polychemotherapy

Molderings G. Naunyn-Schmiedeberg’s Arch Pharmacol 2016
Treatment of Anaphylaxis
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, bronchodilatory, iontropic 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
Extended Observation to Detect Biphasic Anaphylaxis: Number Needed to Treat

Severe Initial Anaphylaxis Symptoms

- Severe initial anaphylaxis symptoms
- Biphasic OR 2.11 (95% CI, 1.32-3.61)
- NNT = 41 (18-195)

Multiple Epinephrine Doses

- Multiple Epinephrine doses
- Biphasic OR 4.82 (95% CI, 2.7 – 8.5)
- NNT = 13 (7 - 27)

Anaphylaxis - 2019 practice parameter update
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
Acute Treatment

- Systemic Hives
  +/- GI Respiratory Symptoms w/o Hypotension
  - Anti-Histamines
  - Consider Epinephrine

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

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

Prophylaxis
- Immunotherapy: Environmental, Food, Hymenoptera
- Anti-IgE
- Tyrosine Kinase Inhibitor (Clonal Mast cell Diseases)
- Desensitization
A Desensitization for Anaphylaxis

Indications: Type 1 - IgE / Non IgE

1) Food Allergies
   Peanuts
   Milk
   Egg
   Tree Nuts

2) Drugs
   Chemotherapy, Platins, Taxanes, Others
   Monoclonals, Chimeric, Humanized, Fully Human
   Antibiotics, Beta Lactams, Others
   Asprin
   Progesterone
   Others

3) Hymenoptera Venom

Relative Contraindications • Severe Asthma
• Cardiovascular Disease
• β-Blockers
• ACE Inhibitors
The Future
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

**FIG 1.** Ibrutinib reduces or eliminates SPT size in as few as 2 doses. Graphs depict the area for the wheal (A; n = 25) and flare (B; n = 25) of SPTs to all foods for all subjects. Bars indicate mean ± SD. Red circles are SPTs performed while subjects were taking ibrutinib, and black circles represent SPTs that were performed before (at baseline) or after ibrutinib treatment. Histamine control SPT results are shown for all subjects in C (wheal; n = 6) and D (flare; n = 6). F/u, Follow-up. Data were analyzed using Friedman tests and Wilcoxon signed rank tests. ***P < .001; ****P < .0001.

**FIG 2.** Ibrutinib abrogates IgE-mediated, but not non-IgE-mediated, basophil activation after just 2 doses. BATs using anti-FcεRI antibody (top, n = 6) or FMLP (bottom; n = 6) stimulation are shown for all subjects at all time points. Red circles are BATs performed while subjects were taking ibrutinib, and black circles represent BATs that were performed before (at baseline) or after ibrutinib treatment. FMLP, N-formyl-L-methionyl-L-leucyl-phenylalanine; f/u, follow-up. Data were analyzed using repeated-measures ANOVA and paired Student t tests. ***P < .001; ****P < .0001.
Scientists Discover Immune Cell Subtype in Mice That Drives Allergic Reactions

NIH–Funded Study Suggests Targeting Cell May Help Prevent Anaphylaxis in Humans

August 1, 2019

Allergies can be life-threatening when they cause anaphylaxis, an extreme reaction with constriction of the airways and a sudden drop in blood pressure. Scientists have identified a subtype of immune cell that drives the production of antibodies associated with anaphylaxis and other allergic reactions. The research was funded by the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, and reveals a potential target for new therapies to prevent severe allergic reactions. The findings are published online today in the journal Science.

Investigators at Yale University, New Haven, Connecticut, the Jackson Laboratory for Genomic Medicine, Farmington, Connecticut, and their collaborators discovered a subtype of T cell—called T follicular helper cell 13, or Tfh13 cells—in laboratory mice and humans. Tfh13 cells drive the immune responses necessary to generate a type of antibody called IgG1, which are key to immediate allergy reactions such as anaphylaxis.
Thirteen is the charm in anaphylaxis

- Gowthaman et al. discovered a subset of T follicular helper cells (T\(_{FH}13\)) that direct B cells to generate high-affinity IgE.
- T\(_{FH}13\) cells are induced by allergens but not during parasite infection.
- Transgenic mice lacking these cells show impaired production of high-affinity, anaphylactic IgE.
- T\(_{FH}13\) cells, which are elevated in patients with food and aeroallergies, may be targeted in future antianaphylaxis therapies.

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 radiocontrast 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?

  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