Anaphylaxis

The Meat Lover's Version

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Disclosures

The speaker has no relevant financial relationships with the manufacturers(s) of any commercial products(s) and/or provider of commercial services discussed in this CME activity

The speaker does not intend to discuss an unapproved/investigative use of a commercial product/device in this presentation.

Agenda

- How to recognize Anaphylaxis
- Management
- Risk factors
- Causes of Anaphylaxis
- Early Peanut Introduction “EPI” program

What is Anaphylaxis ?

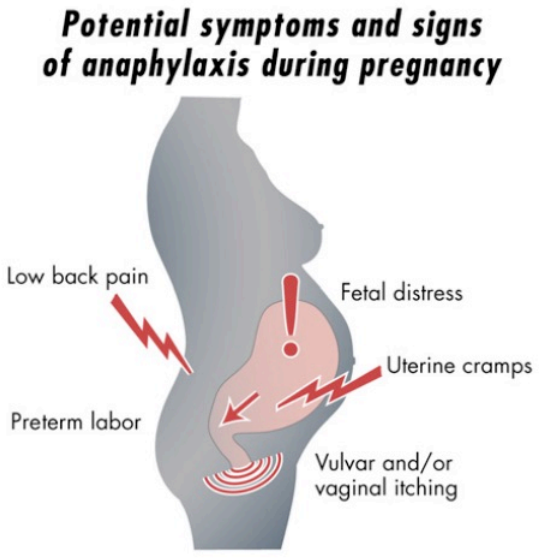
Anaphylaxis is an acute life-threatening systemic hypersensitivity reaction with varied mechanisms, clinical presentations, resulting from the release of mediators from mast cells and/or basophils

WAO Guidelines
AAAAI/ACAAI Guidelines
EAACI Guidelines

Signs and Symptoms of Anaphylaxis

		Percentage
Cutaneous		
Urticaria or angioedema		85-90
Flushing	45-55	
Pruritus without rash		2-5
Cardiorespiratory		
Upper airway angioedema		50-60
Dyspnea, wheeze	45-50	
Dizziness, syncope, hypotension		30-35
GI		
N/V, cramping, diarrhea		25-30
Miscellaneous		
Headache		5-8
Chest pain		4-6
Seizure		1-2
Metallic taste, Aura of impending doom		?

JACI September 2010 Anaphylaxis Practice Parameter



Simons, E JACI September 2012

Differential Diagnosis of Anaphylaxis

- Non-anaphylactic shock (cardiogenic, sepsis, hypovolemic, neurogenic)
- Syncope
- Hereditary or ACEI Angioedema
- Vocal Cord Dysfunction
- Flushing syndromes
- Respiratory distress : asthma, PE
- Panic Attacks / Munchausen syndrome

When to call it Anaphylaxis

Two or more of the following organ systems involved in acute setting

- Cutaneous (required if no known allergen trigger)
- Respiratory
- Circulatory / hypotension
- GI (only if exposed to a LIKELY allergen)*

OR

Exposure to a known allergen followed by

- Circulatory / hypotension

Anaphylaxis ≠ Shock

Strong Recommendation: C Evidence

Management

	Recommendation	Evidence
• Assessment of ABCs	Strong	C
• Supine or reclined position (pregnant patients on their left side)	Moderate	C
• Supplemental O2 for any cardio/respiratory sxs or if decreased O2 SAT	Moderate	D
• Administer epinephrine IM to anterolateral thigh	Strong	B
• Rapid infusion (IV or IO) NS with large bore catheters	Strong	B
• Consider IV epinephrine in monitored setting if not responding to IM	Moderate	C
• Give additional vasopressors (glucagon if on β blockers if not responding to parenteral epinephrine and IV fluids)	Moderate	B
• Administer inhaled β-agonist for bronchospasm	Moderate	B
• H1/H2 blockers and steroids are adjunctive but Don't replace epinephrine	Strong	B

Management

	Recommendation	Evidence
• Assess risk factors for severe or fatal anaphylaxis	Moderate	B
• Identify anaphylaxis triggers for the patient to avoid	Moderate	C
• Prescribe Self injectable epinephrine (SIE) with an written action plan with instructions on administration	Strong	C

respiratory or circulatory or GI symptoms
Remove exposure to any suspected trigger: IV medication or transfusion
Call for assistance

Managing Acute Anaphylaxis

Assess circulation, airway, and breathing
Place patient in semi recumbent or supine position if comfortable
Epinephrine IM injection, repeat every 5-15 minutes according to response, keep systolic BP > 90 mm Hg

Epinephrine IM Auto-injector	
Adult (>25 kg, 55 lb)	**Pediatric (12-25kg, 26-55 lb)**
0.3 mg Epinephrine IM	0.15 mg Epinephrine IM

High flow oxygenation (up to 100%, 6-8 L/min) by mask
Rapid fluid resuscitation if systolic BP < 90 mm Hg

Rapid Normal Saline IV Bolus	
Adult	**Pediatric**
1 – 2 Liters	20 ml/kg, repeat if hypotensive

Nebulized albuterol for bronchospasm
Administer antihistamines (diphenhydramine, and famotidine or ranitidine)

Antihistamines	
Adult	**Pediatric**
phenhydramine 25-50mg IV/IM	Diphenhydramine 1mg/kg IV/IM, max 50mg
motidine 20mg IV OR nitidine 50mg IV	Famotidine 0.25-0.5 mg/kg OR Ranitidine 2-4 mg/kg

Refractory hypotension: IV epinephrine infusion with continuous monitoring. Adults 1-4 mcg/min with max dose 10 mcg/min, pediatric 0.1 mcg/**kg**/min initially
CPR if indicated
If **unresponsive due to beta blockade**: Glucagon 1-5 mg slow IV, then 5-15 mcg/min
Methylprednisolone (solumedrol) 1-2 mg/kg IV (40, 80, or 120 mg vials)

KAISER PERMANENTE.

respiratory or circulatory or GI symptoms
2. Remove exposure to any suspected trigger: IV medication or transfusion
3. Call for assistance

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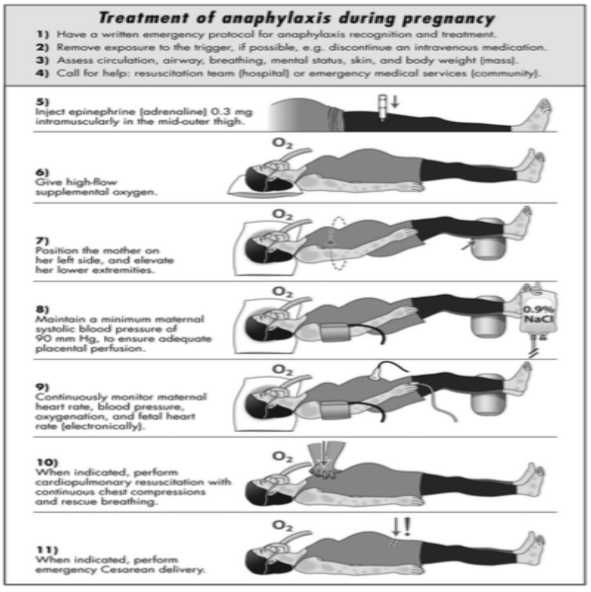
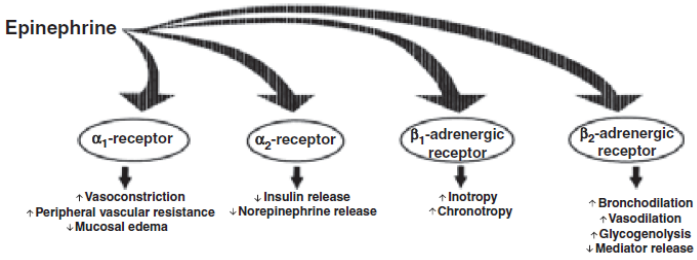
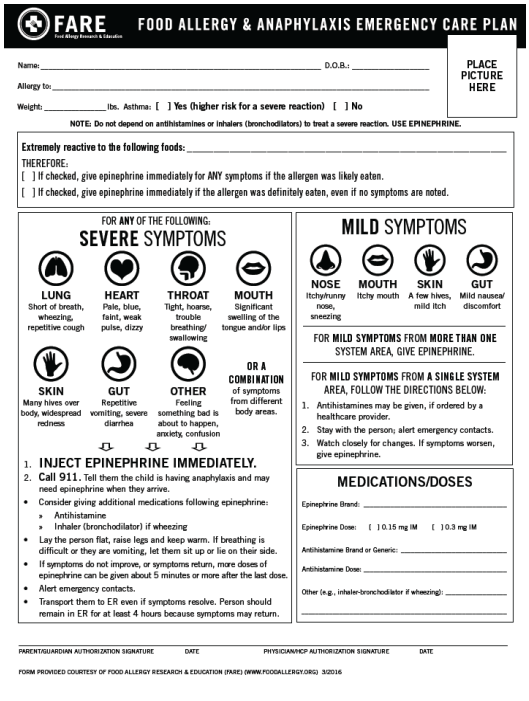


Simons, E Anaphylaxis during pregnancy JACI 2012;130:597-606

Epinephrine is the Drug of Choice for Anaphylaxis



- Self injectors Fixed doses : 0.15 mg and 0.3 mg
- Delay in administration reduces efficacy and is related with higher fatality from anaphylaxis
- UK study : only 14% of anaphylaxis fatalities received epinephrine before cardiac arrest
- Consensus: no absolute contraindication to administer epinephrine during anaphylaxis
- " Sooner rather than later "



FARE FOOD ALLERGY & ANAPHYLAXIS EMERGENCY CARE PLAN

Name: _____ D.O.B.: _____

Allergy to: _____

Weight: _____ lbs. Asthma: [ ] Yes (higher risk for a severe reaction) [ ] No

PLACE PICTURE HERE

NOTE: Do not depend on antihistamines or inhalers (bronchodilators) to treat a severe reaction. USE EPINEPHRINE.

Extremely reactive to the following foods: _____

THEREFORE:

[ ] If checked, give epinephrine immediately for ANY symptoms if the allergen was likely eaten.

[ ] If checked, give epinephrine immediately if the allergen was definitely eaten, even if no symptoms are noted.

FOR ANY OF THE FOLLOWING:

SEVERE SYMPTOMS

- **LUNG** Short of breath, wheezing, repetitive cough
- **HEART** Pale, blue, faint, weak pulse, dizzy
- **THROAT** Tight, hoarse, trouble breathing/ swallowing
- **MOUTH** Significant swelling of the tongue and/or lips
- **SKIN** Many hives over body, widespread redness
- **GUT** Repetitive vomiting, severe diarrhea
- **OTHER** Feeling something bad is about to happen, anxiety, confusion

OR A COMBINATION of symptoms from different body areas.

1. **INJECT EPINEPHRINE IMMEDIATELY.**
2. **Call 911.** Tell them the child is having anaphylaxis and may need epinephrine when they arrive.
- Consider giving additional medications following epinephrine:
  - » Antihistamine
  - » Inhaler (bronchodilator) if wheezing
- Lay the person flat, raise legs and keep warm. If breathing is difficult or they are vomiting, let them sit up or lie on their side.
- If symptoms do not improve, or symptoms return, more doses of epinephrine can be given about 5 minutes or more after the last dose.
- Alert emergency contacts.
- Transport them to ER even if symptoms resolve. Person should remain in ER for at least 4 hours because symptoms may return.

MILD SYMPTOMS

- **NOSE** Itchy/runny nose, sneezing
- **MOUTH** Itchy mouth
- **SKIN** A few hives, mild itch
- **GUT** Mild nausea/ discomfort

FOR **MILD SYMPTOMS** FROM **MORE THAN ONE** SYSTEM AREA, GIVE EPINEPHRINE.

FOR **MILD SYMPTOMS** FROM **A SINGLE SYSTEM** AREA, FOLLOW THE DIRECTIONS BELOW:

1. Antihistamines may be given, if ordered by a healthcare provider.
2. Stay with the person; alert emergency contacts.
3. Watch closely for changes. If symptoms worsen, give epinephrine.

MEDICATIONS/DOSES

Epinephrine Brand: _____

Epinephrine Dose: [ ] 0.15 mg IM [ ] 0.3 mg IM

Antihistamine Brand or Generic: _____

Antihistamine Dose: _____

Other (e.g., inhaler-bronchodilator if wheezing): _____

_____

PARENT/GUARDIAN AUTHORIZATION SIGNATURE DATE PHYSICIAN/NP/CP AUTHORIZATION SIGNATURE DATE

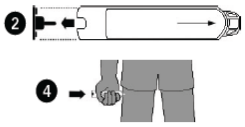
FORM PROVIDED COURTESY OF FOOD ALLERGY RESEARCH & EDUCATION (FARE) (WWW.FOODALLERGY.ORG) 3/2016

FARE Food Allergy Research & Education

FOOD ALLERGY & ANAPHYLAXIS EMERGENCY CARE PLAN

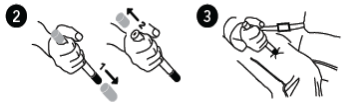
EPIPEN® (EPINEPHRINE) AUTO-INJECTOR DIRECTIONS

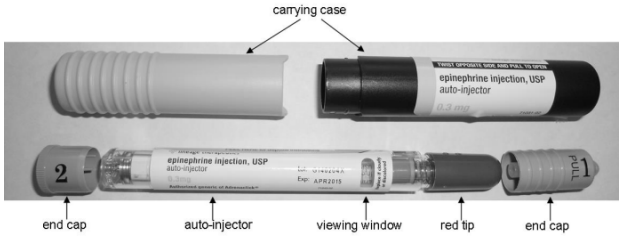
1. Remove the EpiPen Auto-Injector from the plastic carrying case.
2. Pull off the blue safety release cap.
3. Swing and firmly push orange tip against mid-outer thigh.
4. Hold for approximately 10 seconds.
5. Remove and massage the area for 10 seconds.

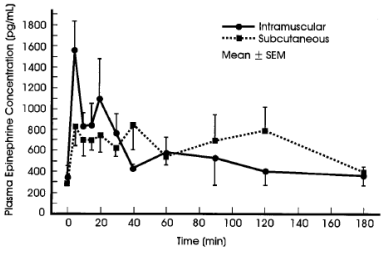


ADRENACLICK®/ADRENACLICK® GENERIC DIRECTIONS

1. Remove the outer case.
2. Remove grey caps labeled "1" and "2".
3. Place red rounded tip against mid-outer thigh.
4. Press down hard until needle penetrates.
5. Hold for 10 seconds. Remove from thigh.







Higher plasma epinephrine levels via IM vs SubQ route

IM epinephrine to the thigh is superior to IM or Subq to the arm

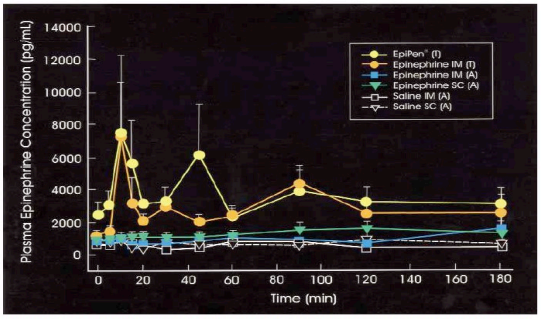


FIG 1. Mean plasma epinephrine concentrations versus time are shown after administration of an identical 0.3-mg (0.3-mL) dose of epinephrine by IM or SC injection in 2 different sites. *T*, Thigh; *A*, upper arm. Mean endogenous plasma epinephrine concentrations are shown after IM or SC injection of 0.9% saline solution (0.3 mL) in the upper arm. The plasma epinephrine concentrations shown were calculated by averaging (mean ± SEM) the epinephrine concentrations at each sampling time for each route and each site of injection.

Adequacy of the epinephrine autoinjector needle length in delivering epinephrine to the intramuscular tissues

Ted T. Song, DO*; Michael R. Nelson, MD, PhD*; James H. Chang, MD†; Renata J. M. Engler, MD*; and Badrul A. Chowdhury, MD, PhD*

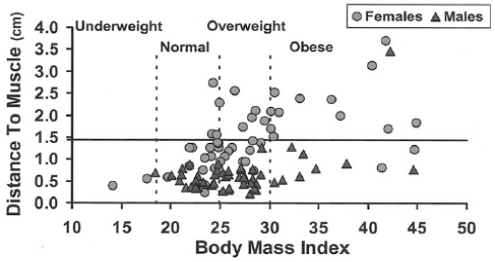


Figure 2. Scatterplot of the distance to muscle vs body mass index for men and women. Dashed vertical lines are drawn to identify the body mass index categories. The horizontal line indicates the length of the epinephrine auto-injector needle length of 1.43 cm. Individuals above the 1.43-cm line would most likely receive subcutaneous epinephrine.

Percentage DTM (distance to muscle) > 1.43 cm (Epipen needle length)

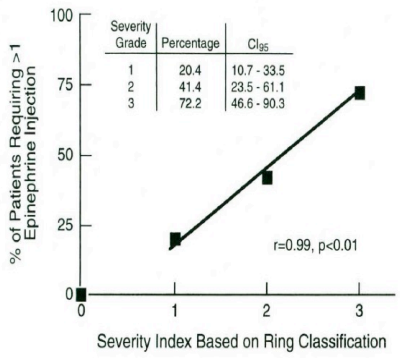
	DTM	DTM under compression
Male	2%	2%
Female	42%	28%

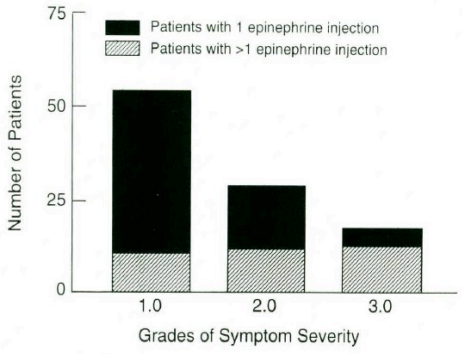
Almost 30% of females using Epipen receive subcutaneous dosing instead of IM

Ann Allergy Asthma Immunol. 2005;94:539–542.

How many doses of Epinephrine are needed for anaphylaxis ?

1/3rd of anaphylaxis reactions needed 2 or more doses





Korenblat, P Allergy and Asthma Proc 1999 20:383-386

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

CLINICAL REPORT

Self-injectable Epinephrine for First-Aid Management of Anaphylaxis

Guidance for the Clinician in Rendering Pediatric Care

Scott H. Sicherer, MD, F. Estelle R. Simons, MD, and the Section on Allergy and Immunology

TABLE 2 Epinephrine Autoinjectors for Infants and Children: Dilemmas in Dosing and Possible Solutions[19]

Patient's Weight, kg (lb)	Optimal Dose (0.01 mg/kg), mg	Availability of Autoinjector[a]	Alternatives/Implications[b]	Comments/Recommendations[c]
≤10 (≤22)	≤0.10	No	Fixed-dose 0.15-mg autoinjector provides ≥1.5-fold overdose; ampule/syringe/needle technique may lead to delay in injection and inaccurate dosing	Evaluate degree of overdose vs ability to use ampule/syringe/needle; no specific evidence base for decision except that ampule/syringe/needle technique is delay and error prone, and autoinjector (0.15 mg) is more commonly prescribed for infants by physicians forced to choose
15 (33)	0.15	Yes	0.15-mg autoinjector provides optimum dose	Prescribe autoinjector (0.15 mg)
20 (44)	0.20	No	0.15-mg autoinjector provides 1.3-fold underdose; 0.30-mg autoinjector provides 1.5-fold overdose	Usually prescribe 0.15-mg autoinjector, but increasing weight of child over 20 kg and high risk on the basis of clinical history[d] may be considered an appropriate rationale for prescribing a 0.30-mg autoinjector
25 (55)	0.25	No	0.15-mg autoinjector provides 1.7-fold underdose; 0.30-mg autoinjector provides 1.2-fold overdose	Usually prescribe 0.30-mg autoinjector; a small overdose in a healthy child generally carries a low risk of adverse effects compared with the risk of an underdose during anaphylaxis
≥30 (≥66)	0.30	Yes	0.30-mg autoinjector provides optimum dose	Prescribe autoinjector (0.30 mg)

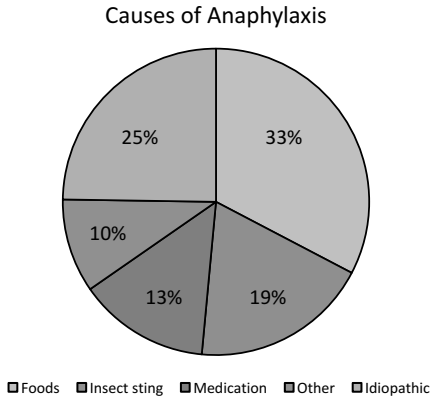
Pediatrics March 2007

Indication for Self Injectable Epinephrine (SIE)

Clinical Situation	Risk of future anaphylaxis	Rx for Epinephrine
Large local Sting Rxn	5 – 10%	SDM
Oral Allergy Syndrome	2 – 10%	SDM
Contact hives (no SR) from food	?	SDM
SR w/ underlying Cardiovascular disease	?	yes

SDM Shared Decision Making
SR Systemic Reaction

Etiology of Anaphylaxis
Rochester Minnesota 1990 - 2000



Decker, W JACI 2008;122:1161-5

" Other " causes of anaphylaxis

- Latex allergy
- Radiocontrast Media Reactions
- Cold induced
- Exercise induced Anaphylaxis
- Food Associated Exercise Induced Anaphylaxis
- Scombroid poisoning
- Seminal fluid allergy
- Mastocytosis

Radiocontrast Media Reactions

- Considered Non-IgE mediated " anaphylactoid " reactions
- Incidence: 1 % of RCM administration have moderate reactions
  0.1% have life-threatening reactions
- Totally Unrelated to seafood allergy, topical iodine application
- RCM Reaction Risk factors: prior RCM reaction (up to 44%) , asthma, atopy
- More severe reaction : Beta blocker use, cardiovascular disease

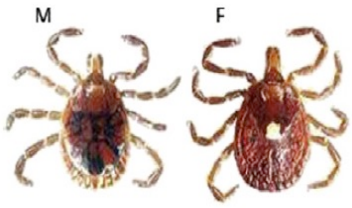
Management of RCM Reactors

- Low or iso-osmolar RCM
- Prednisone 50 mg at 13, 7, and 1 hour before procedure
- Diphenhydramine 50 mg (PO or IM) 1 hour before procedure
- Emergent RCM procedure pretreatment:
  200 mg hydrocortisone IV, then every 4 hours till RCM given
  50 mg diphenhydramine IM 1 hr before RCM given

Lieberman,P Ann Allergy Asthma Immunol November 2015

Delayed Anaphylaxis to Red Meat Masquerading as Idiopathic Anaphylaxis

- Alpha-gal (galactose-alpha-1,3-galactose) is a blood group oligosaccharide found in nonprimate mammals
- Lone Star Tick bites can result in sensitization to alpha-gal antigen presenting as delayed anaphylaxis 3-5 hours after ingestion of red meat (beef,pork,lamb, deer)
- IgE to alpha-gal also cross reacts to the Fab portion of the mAb Cetuximab resulting in allergic reactions even on the first exposure



Oral Mite Anaphylaxis (OMA) aka Pancake Syndrome

- Severe allergic reactions after ingestion of mite contaminated wheat flour or corn meal
- Common foods: pancakes, beignets, pizza dough, scones, …
- Ingestion of storage mites that cross react with dust mites, heat stabile mite allergens trigger IgE mediated anaphylaxis in sensitized persons

Takoyaki

Okonomiyaki

Oral Mite Anaphylaxis (OMA) aka Pancake Syndrome

Risk Factors

- Underlying atopic condition
- Mite allergic
- Tropical or subtropical climate
- NSAID sensitivity ?

Diagnosis

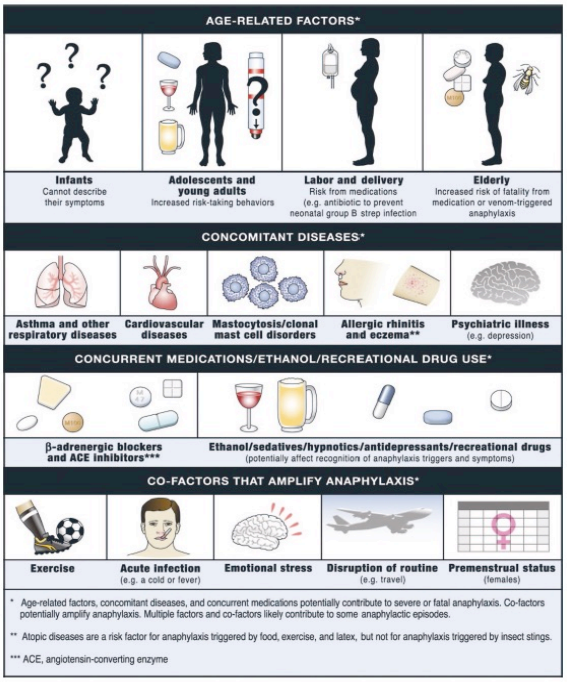
- Demonstrate mite specific allergy
- Negative work up for wheat allergy , tolerance to other wheat foods
- Skin test reactivity to incriminated flour if available
- Microscopic identification of mites in suspected flour sample

Prevention

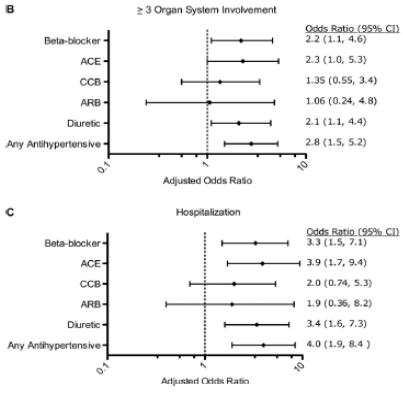
- Store flour in refrigerator or freezer
- Avoid cooking with expired flour products
- Carry emergency medications for anaphylaxis
- Desensitization ?

Sanchez, M JACI Jan 2013

Patient related factors that contribute to occurrence or severity of anaphylaxis



Antihypertensive medication use is associated with increased organ system involvement and hospitalization in emergency department patients with anaphylaxis



Lee, S JACI April 2013

Anaphylaxis severity risk and Hospitalization are increased

- Beta Blocker
- ACEI
- Diuretics
- Any Antihypertensive

Should β-blockers be given to patients with heart disease and peanut-induced anaphylaxis? A decision analysis

Risk models show increased survival in post-MI or CHF using Beta blockers EVEN IF at risk of peanut anaphylaxis

Tenbrook, J JACI May 2004

Fatality Registry from Food Anaphylaxis 2001-2006
80% had a history of nut or peanut allergy
> 70% had asthma
70% did not get Epinephrine in a timely manner

TABLE I. Food fatalities 2001-2006

Patient no.	Age (y)	M/F	Date	Culprit	Asthma	Previous history	Food	Location	Timely epinephrine
1	32	M	3/11/2001	Nuts	Yes	Yes	Nut bowl	Restaurant	No
2	16	M	5/9/2001	Walnut	Yes	Yes	Chinese food	School, cooking class	Probably
3	9	M	5/18/2001	Peanut	Yes	Yes	Cookie	School outing	No
4	24	F	11/26/2001	Peanut	Yes	Yes	Chinese food	Home	No
5	25	F	10/30/2001	Nut meats	Yes	Yes	Candy	Home of friends	No
6	16	M	11/5/2002	Milk	Yes	Yes	Bread	Home	Unk
7	31	M	12/13/2002	Peanut	Yes	Yes	Catered food	Office party	No
8	50	M	12/24/2002	Nut	Yes	Yes	Cookie	Home	No
9	12	F	3/14/2003	Peanut	Unk	Unk	Egg roll	Unk	Unk
10	18	M	6/21/2003	Peanut	Unk	Unk	Wrap	Unk	Unk
11	32	M	3/15/2003	Shrimp	Yes	Yes	Meal	Restaurant	No
12	29	M	6/13/2003	Peanut	Yes	Yes	Meal	Restaurant	No
13	29	M	4/24/2000	Almond	Yes	Yes	Candy	Office	Yes
14	17	F	12/26/1986	Nuts	Yes	Yes	Cookie	Home of friends	No
15	21	F	10/9/2003	Peanut	Yes	Yes	Brownie	College	No
16	18	M	1/20/2004	Shrimp roll	Yes	Unk	Shrimp roll	Restaurant	No
17	27	M	2/1/2004	Peanut	Unk	Yes	Baked clam	Home	No
18	17	M	2/8/2004	Hazelnut	Yes	Yes	Candy	Home of friends	No
19	17	F	4/6/2004	Peanut	Yes	Yes	Peanut butter	Camp	No
20	34	F	5/29/2004	Peanut	Unk	Yes	Thai dish	Home	No
21	5	M	8/1/2004	Peanut	Unk	No	Peanuts	Home	No
22	9	M	7/22/2004	Milk	Unk	Unk	Milk	Camp	Yes
23	22	F	10/29/2004	Peanut	Yes	Yes	Dessert	Restaurant	No
24	14	F	1/22/2005	Peanut	Yes	Yes	Egg roll	Restaurant	No
25	36	M	3/21/2001	Peanut	Yes	Yes	Brownie	Work	No
26	17	M	3/5/2005	Milk/whey	Yes	Yes	Protein shake	Home	No
27	7	F	3/2/2005	Milk	Yes	Yes	Chocolate mix	Home	Unk
28	11	F	5/31/2005	Peanut	Unk	Yes	Candied apple	Carnival	Unk
29	40	M	2/8/2006	Tree nut	Unk	Yes	Cookie	Work	Yes
30	13	F	4/13/2006	Peanut	Yes	Yes	Wrap	Fast food in mall	No
31	16	M	8/1/2006	Peanut	Yes	Yes	Cookie	Home of friends	No

F, Female; *M*, male; *Unk*, unknown.

Biphasic Anaphylaxis

- Definition: Recurrence of symptoms within 72 hours after the initial anaphylactic event, without re-exposure to the trigger

A 2015 Systematic Review / Meta-analysis of 27 studies (N=4162) showed …

- Biphasic anaphylaxis (BA) occurred in 4.6% of cases of anaphylaxis
- Median time for BA to occur was 11 hours after index event
- Hypotension OR Unknown trigger were risk factors for BA
- Food allergy trigger was less likely to cause BA
- No clear protective effect regarding dose and timing of epinephrine or oral steroids with risk of having BA
- Observation period at least 4 – 8 hours, adjust for risk factors

Lee, S JACI Pract 2015;3:408-16
Campbell, R Ann Allergy Asthma Immunol 113;2014 :599-608

Mediators of Anaphylaxis

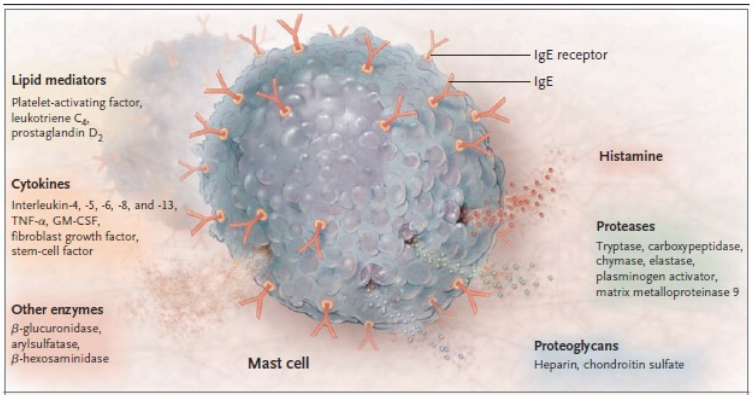
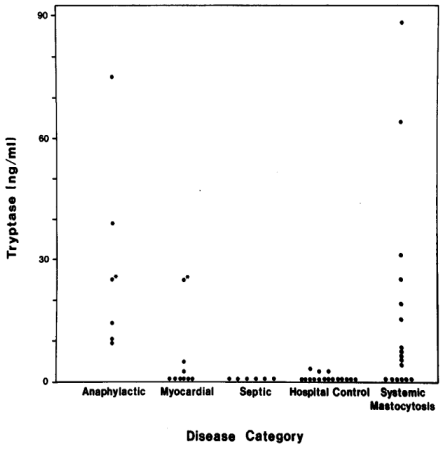


Figure 1. Mediators of Anaphylaxis.

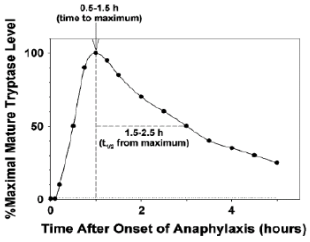
Activation of the IgE receptor on mast cells induces the release of preformed mediators such as histamine and various proteases as well as the synthesis of lipid mediators and cytokines. TNF-α denotes tumor necrosis factor α, and GM-CSF granulocyte–macrophage colony-stimulating factor.

TRYPTASE LEVELS AS AN INDICATOR OF MAST-CELL ACTIVATION IN SYSTEMIC ANAPHYLAXIS AND MASTOCYTOSIS

LAWRENCE B. SCHWARTZ, M.D., PH.D., DEAN D. METCALFE, M.D., JEFFREY S. MILLER, M.D., HARRY EARL, M.D., AND TIMOTHY SULLIVAN, M.D.



- Serum tryptase is a marker of mast cell degranulation
- Tryptase is elevated in 20% of anaphylaxis cases
- Most food anaphylaxis cases have a normal tryptase level
- Helpful if not certain anaphylaxis was the cause
- Persistent elevation suggests mastocytosis



NEJM 1987;316:1622-6

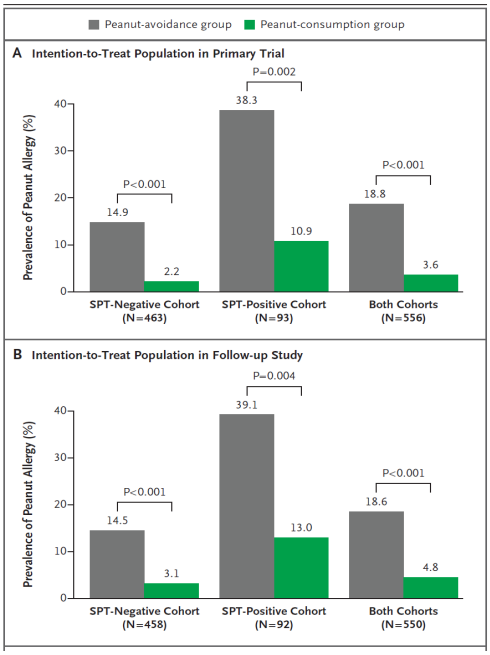
Learning Early About Peanut (LEAP) Allergy Trial

- 640 infants age 4 – 11 months
- RISK of future peanut allergy : eczema or egg allergy present
- Open, Randomized study
- Peanut extract Skin Prick Test (SPT) either negative or mild positive (1 – 4mm wheal)
- Early introduction of peanut up to age 5 y/o vs peanut avoidance

NEJM Feb 2015 372;9:803-13

LEAP and LEAP follow up

- NNT = 7.1
- Relative risk reduction = 80%
- Absolute Risk Reduction = 14%



NEJM Feb 2015 372; 9:803-13
NEJM April 2016 374;15:1435-43

Early Peanut Introduction (EPI) Program For KP HI

- Criteria — age 4 – 11 months; Eczema or Egg allergy
- Outreach letter — February 2016
- RN screening
- Allergy visit for peanut skin testing
- Oral peanut challenge if indicated
- Regular peanut ingestion to age 5 years old

Summary

- " Two organ systems " can recognize anaphylaxis, most have cutaneous sxs
- Epinephrine IM is your first medication, " Sooner rather than Later "
- Use 0.3mg epinephrine IM for ≥ 55 lbs (25 kg) - adults
- H1/H2 blockers and corticosteroids DO NOT replace epinephrine
- Risk factors : Beta blocker/ACEI, cardiorespiratory disease, nut allergy, biphasic pattern
- Consider tryptase level acutely if not certain of diagnosis
- Give anaphylaxis action plan along with epinephrine injector instruction