

Severe Food Allergy – Prediction & Approach to Treatment

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Faculty Disclosures

FINANCIAL INTERESTS

I have disclosed below information about all organizations and commercial interests, other than my employer, from which I or a member of my immediate family or household receive remuneration in any amount

Name of Organization	Nature of Relationship
Allertin Therapeutics, LLC	Consultant, Minority Stockholder
University of Nebraska	Consultant
Food Allergy Initiative	Scientific Advisor
Danone Scientific Advisory Board	Scientific Advisor

RESEARCH INTERESTS

I have disclosed below information about all organizations which support research projects for which I or a member of my immediate family or household serve as an investigator.

Name of Organization	Nature of Relationship
National Institutes of Health	Grantee
Food Allergy Initiative	Grantee

• Patents – EMP-123 (recombinant protein vaccine) & FAHF-2 (herbal product)

Food Allergy and Anaphylaxis

Anaphylaxis

- Olmstead County, MN, experience
 - 30 → 50 cases/100,000 from early '90's to early 2000
 - ~1/3 of cases due to food allergy

Yocum et al. JACI 1999; 104:452-456; Decker et al. JACI 2008; 122:1161-1165

- Extrapolated U.S. experience [Population - 305 Million]:
 - ~32,000 cases / year → 53,700 cases / year

- FDA NEISS [34 EDs; 2 mo period]: ED visits / year in US
 - food allergy: ~125,000 (or ~1 ED visit every 3 minutes)
 - anaphylaxis: ~14,000 hospitalizations: ~3,100

Ross et al. JACI 2008; 121:166-171

Food-induced Anaphylaxis Prevalence

- Pediatric ED visits for food-induced anaphylaxis between 2001-2006 Children's Hospital in Boston

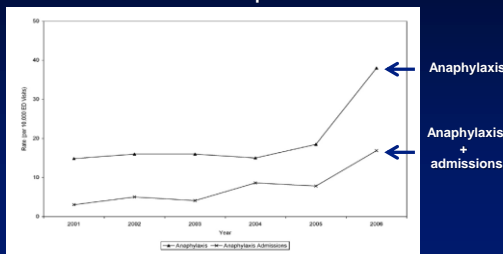
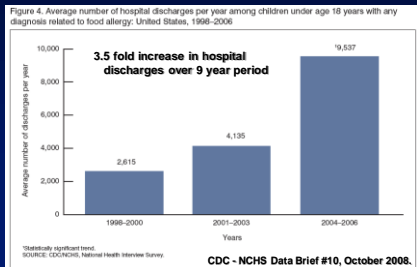


FIG 1. Annual rates of ED visits and hospitalizations for food-induced anaphylaxis (2001-2006).

Rudders et al. JACI 2010

CDC Brief on Food Allergy in US

- ~4% of children <18 yrs have food allergy



Statistically significant trend.

SOURCE: CDC/NCHS, National Health Interview Survey

CDC - NCHS Data Brief #10, October 2008.

NIH-FAAN Consensus Meeting: Definition of Anaphylaxis

Attended by allergists/immunologists, emergency department physicians, anesthesiologists, primary care physicians, emergency medical technicians, lay personnel, and basic scientists representing over 12 organizations

Generalized allergic reaction that is rapid in onset and may progress to death.

Sampson et al. JACI 2006;117(2):391-397.

Criteria for Diagnosing Anaphylaxis NIH / FAAN Working Group

Anaphylaxis is likely when any one of the three following sets of criteria are fulfilled:

1. Acute onset of an illness (mins to hrs) with involvement of skin/mucosal tissue plus airway compromise &/or symptoms of reduced blood pressure
2. Two or more of the following that occur rapidly after exposure to a **likely allergen for that patient** (mins to hrs): skin/mucosal tissue, airway compromise, reduced BP, &/or persistent GI sx's
3. Reduced BP after exposure to **known allergen for that patient** (mins to hrs): > 30% drop from baseline

Sampson et al. *JACI* 2006;117(2):391-97

Grading Severity of Anaphylaxis

Grade	Defined by
(1) Mild (skin & subcu. tissues, GI, &/or mild respiratory)	Flushing, urticaria, periorbital periorbital or angioedema; mild dyspnea, wheeze or upper respiratory symptoms; mild abdominal pain &/or emesis
(2) Moderate (mild sx's + features suggesting moderate respiratory, cardiovasc or GI sx's)	Marked dysphagia, hoarseness, &/or stridor; SOB, wheezing & retractions; crampy abdominal pain, recurrent vomiting &/or diarrhea; &/or mild dizziness
(3) Severe (hypoxia, hypotension, or neurological compromise)	Cyanosis or SpO ₂ ≤ 92%, hypotension, confusion, collapse, loss of consciousness; or incontinence

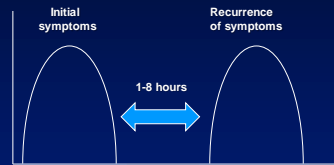
Sampson HA. *Pediatr* 2003;111:1601-1608

Differences in Symptoms by Age

Children	Adults
<ul style="list-style-type: none"> • More generalized allergic reactions • ~80% with cutaneous symptoms • More often respiratory symptoms • Mostly milk, egg, peanut, tree nuts & sesame 	<ul style="list-style-type: none"> • More anaphylaxis • >90% with cutaneous symptoms • More cardiovascular symptoms • Mostly peanuts, tree nuts, shellfish & fish

Time Course of Anaphylaxis

- Rapid onset within seconds to few hours
- Uniphasic, biphasic, or protracted reactions



Lee et al, *Pediatrics* 2000
Lieberman et al, *Ann Allergy Asthma Immunol* 2005

Diagnostic Tests

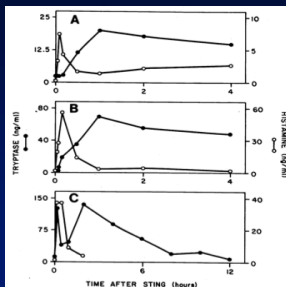


Figure 1. Plasma tryptase (▲) and histamine (○) levels after a bee sting challenge.

Histamine

- Low sensitivity, low specificity
- Increased from 15-60 min
- Needs special handling

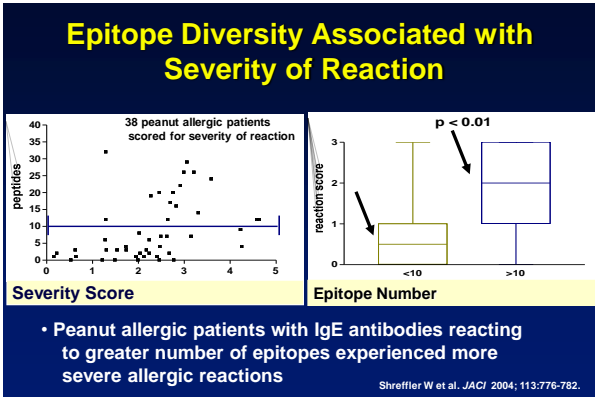
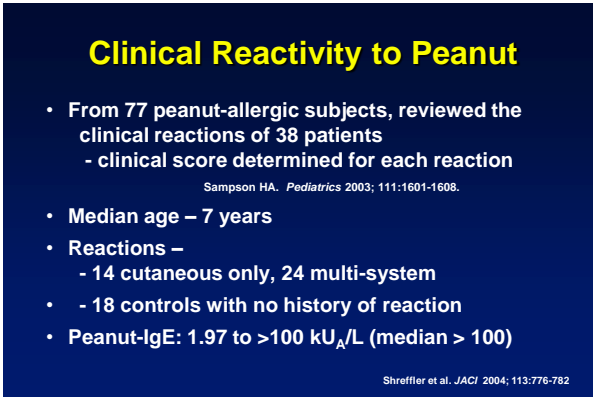
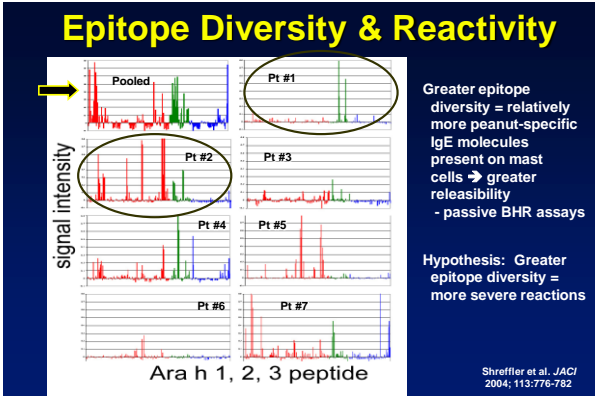
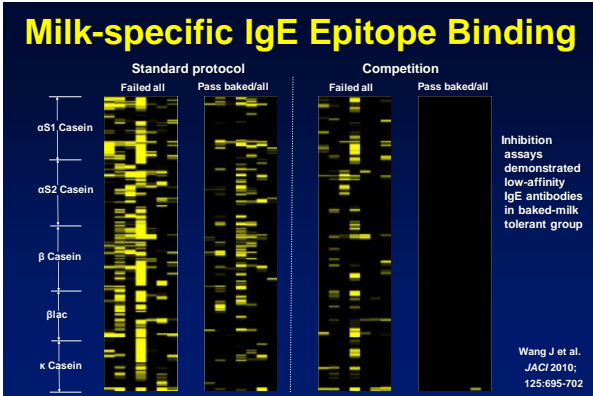
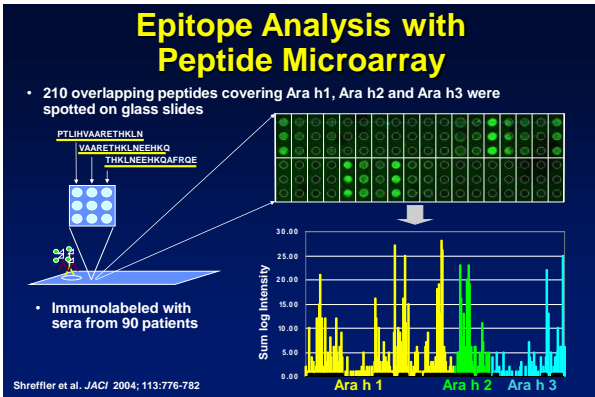
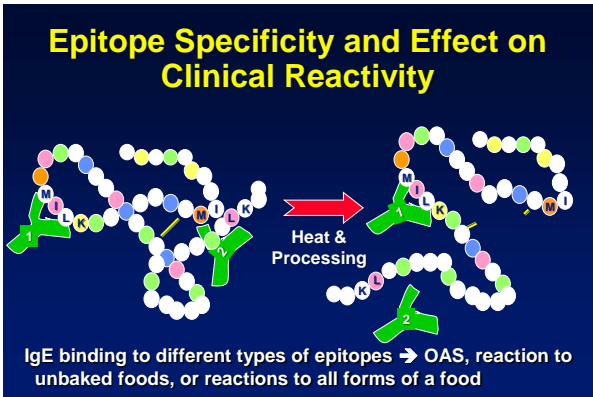
Tryptase

- Low sensitivity, low specificity
- Increased from 15 min-3 hrs
- Rarely increased in food-induced anaphylaxis
- Serial measurements may be helpful

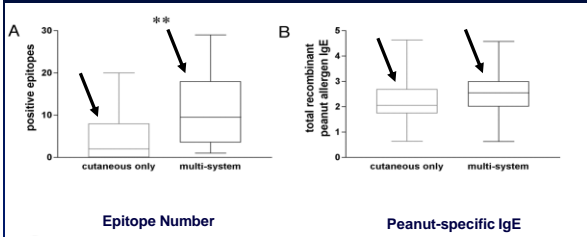
Simons FE, *JACI* 2010; 120 suppl

Predicting Reactivity & Severity

- **Reactivity:** identify those at risk for anaphylaxis
 - History - < 40% of histories confirmed
 - Skin Tests or allergen-specific IgE: < 40% confirmed
 - Food-specific IgE levels: 95% Predictive levels
 - Oral Food Challenge: open, single & double-blind
- **Severity:** identify those requiring emergency plan
 - History – previous severe reaction; asthma; food type; and adjunct factors, e.g. exercise, alcohol, NSAIDs, infections
 - No correlation with PST size or serum IgE level
 - Diversity of epitope recognition
 - Platelet activating factor acetylhydrolase activity



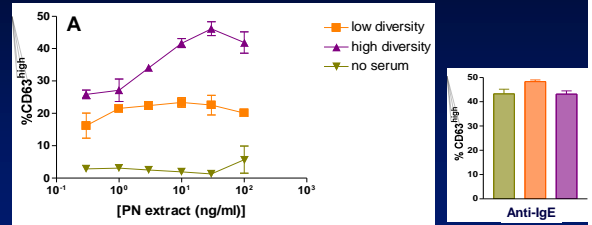
Clinically Reactive Patients



No correlation between severity and total or peanut-specific IgE

Shreffler et al. JACI 2004; 113:776-782

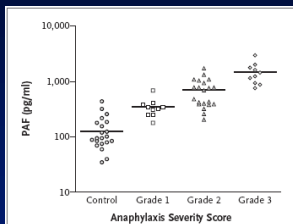
Human Basophil Activation vs Epitope Diversity



Non-atopic Donor PBMC

Shreffler et al. JACI 2004; 113:776-782

Platelet Activating Factor & Anaphylaxis



Increasing PAF levels correlated with increasing severity of anaphylaxis

Figure 2. Serum Platelet-Activating Factor (PAF) Levels as a Function of Anaphylaxis Severity Score. Untransformed values are plotted on a log scale.

Vadas P et al. NEJM 2008; 358:28-35.

PAF Acetylhydrolase Activity & Anaphylaxis

Table 2. Comparison of PAF Acetylhydrolase Activity in Patients with Fatal Peanut Anaphylaxis and Control Groups.*

Variable	Fatal Peanut Anaphylaxis (N=9)	Adult Control (N=49)	Pediatric Control (N=26)	Children with Peanut Allergy (N=63)	Nonfatal Peanut Anaphylaxis (N=24)	Nonanaphylactic Deaths (N=10)
PAF acetylhydrolase activity — nmol/ml/min						
Mean	14.5±3.4	34.9±10.6‡	27.7±8.5‡	25.2±5.7‡	29.7±9.1‡	26.4±7.2‡
Range	9.7–18.6	19.0–59.8	11.4–48.2	14.2–41.0	12.8–45.8	15.2–34.6
PAF acetylhydrolase activity ≤20 nmol/ml/min — no. (%)	9 (100)	1 (2)‡	4 (15)‡	13 (21)‡	5 (21)‡	3 (30)‡

* PAF denotes platelet-activating factor. Plus-minus values are means ±SD.

‡ P<0.001 for the comparison with the fatal-peanut-anaphylaxis group.

‡ P<0.01 for the comparison with the fatal-peanut-anaphylaxis group.

Vadas P et al. NEJM 2008; 358:28-35

• but no difference when measured in post-anaphylaxis healthy state
Bansal AS et al. NEJM 2008; 358:1516-1517.

Anticipating the Severity of an Anaphylactic Reaction

- Severity affects type of therapeutic intervention and recommendations for dealing with future reactions
- Many reactions resolve spontaneously
- Progression of symptoms affected by source of allergen and varies among individuals
- No evidence to support concept that reactions worsen with each successive exposure
 - reactions tend to be highly variable
- Factors increasing risk of severe reaction: age, asthma, allergen, & use of β -blockers

Clinical Features & Predicting Severity of Anaphylaxis

- Reviewed 1,149 systemic hypersensitivity reactions presenting to hospital emergency department
 - analyzed general, skin, GI, respiratory, cardiovascular & neurological symptoms
- Most frequent symptoms:
 - urticaria & flushing (73%) > pruritus (48%) > angioedema (39%) > dyspnea (29%) > chest or throat tightness (24%) > nausea & wheeze (13%) > vomiting & dizziness [pre-syncope] (10%)
- Compared symptoms to development of severe anaphylaxis – cyanosis and/or hypotension

Brown SGA. JACI 2004; 114:371-376.

Clinical Features & Severity of Anaphylaxis: Cardiovascular

Logistic regression analysis: minimum set of predictors for documented hypotension, ranked by odds ratio

Clinical Feature	Odds Ratio	P
Incontinence	13.0	0.033
Collapse (including LOC)	6.3	<0.001
Diaphoresis	4.0	<0.001
Cyanosis (SpO ₂ ≤92%)	3.4	0.010
Vomiting	2.9	0.002
Dizziness (presyncope)	2.7	0.003
Dyspnea	2.1	0.008
Nausea	2.2	0.018

Brown SGA. JACI 2004; 114:371-376.

Clinical Features & Severity of Anaphylaxis: Respiratory

Logistic regression analysis: minimum set of predictors for cyanosis or SpO₂ ≤92%, ranked by odds ratio

Clinical Feature	Odds Ratio	P
Confusion	9.9	0.028
Stridor	3.8	0.008
Dyspnea	2.8	0.003
Hypotension	2.9	0.013
Wheeze	2.2	0.028

Brown SGA. JACI 2004; 114:371-376.

Acute Management of Anaphylaxis: NIAID Expert Panel Recommendation

Treatment for food-induced anaphylaxis should focus on the following:

- Prompt and rapid treatment after onset of symptoms
- Intramuscular (IM) **epinephrine** as first-line therapy
- Other treatments, which are adjunctive to epinephrine dosing

These actions should be quickly *followed by* these additional steps:

- Placement of the patient in a recumbent position (if tolerated), with the lower extremities elevated
- Provision of supplemental oxygen
- Administration of IV fluid (volume resuscitation)

Boyce et al. JACI 2010

Epinephrine – What dose?

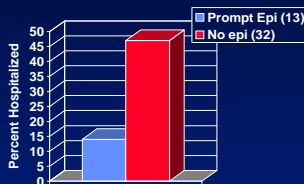
- 0.01mg/kg intramuscular up to 0.5 mg
- 0.15mg = optimal for 15 kg person
- 0.3mg = optimal for 30 kg person
- When to transition doses – weight, reaction history, co-morbid diseases



Simons et al. JACI 2010

Importance of Prompt Epinephrine

- Review of epinephrine use in children (prior anaphylaxis/Epi. Rx)
- Referral population to allergy clinic (n=94)
- 45 episodes anaphylaxis (reaction at school-17%)



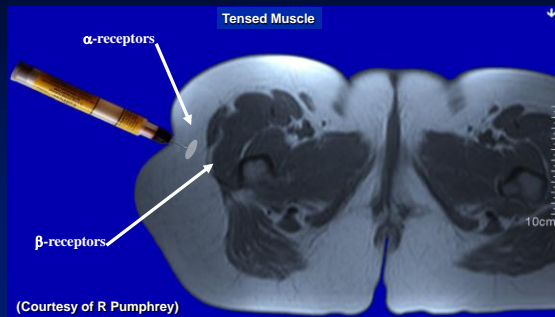
Gold & Sainsbury JACI 2000

Epinephrine is Not Always Effective

- Delayed use
- Suboptimal dose, route or site of injection
- Rapidly progressing anaphylaxis
- Medication that interferes with optimal epinephrine effect – eg. α-adrenergic blocker or β-blocker
- Empty vena cava/empty ventricle syndrome (patients in shock who suddenly sit, stand, or are placed upright)
- 19% required 2 doses of epinephrine; 6% needed 3rd dose

Jarvinen et al. JACI 2008

Adequacy of Auto-injector in Obese Patient



Adjunctive Treatment

Antihistamines

- H1 antihistamines are effective for cutaneous symptoms, but not for respiratory symptoms, gastrointestinal symptoms or shock
- H2 receptor blockers may be given concurrently for added effect

Lieberman et al, JACI 2010

Adjunctive Treatment

Corticosteroids

- Conflicting evidence that steroids may or may not prevent or reduce severity of late phase response

Douglas JACI 1994; Lieberman Annals 2005

- No definitive proof of efficacy – Cochrane review failed to identify any randomized evidence for the effectiveness of steroids in the management of anaphylaxis

Choo, Cochrane Database of Systematic Reviews 2012

Adjunctive Treatment

- Bronchodilator
- IV fluid hydration
- Positioning – supine and legs raised
- Vasopressors
- Glucagon
- Others – oxygen, atropine
- Observe at least 4-6 hours

Discharge Plan

NIAID Expert panel recommendations:

- Written anaphylaxis emergency action plan
- Epinephrine auto-injector (2 doses)
- Plan for monitoring of auto-injector expiration dates
- Plan for arranging further evaluation
- Printed information about anaphylaxis and its treatment

Boyce et al, JACI 2010

Anaphylaxis: Summary

- Anaphylaxis
 - Life-threatening allergic reaction
 - Prompt recognition and treatment
 - Need for diagnostic biomarkers
- Allergic reaction
 - More common, less serious
 - ED treatment based on presentation and clinical judgment