22nd World Allergy Congress

Food Allergy

Advances in Diagnosis

By:

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Food Allergy
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12/4/2011

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 (including consulting fees, grants, honoraria, investments, etc.) or invest money which may create or be perceived as a conflict of interest.

Name of Organization	Nature of Relationship
Allertein Therapeutics, LLC	Consultant, Minority Stockholder
University of Nebraska	Advisory Board
Food Allergy Initiative	Consultant
Immusan T	Advisory Board

- **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)

Developing National Guidelines

- 3/2007 – AAAAI & FAAN initiative
- 3/2008 – NIAID agreed to sponsor a consortium of 34 professional organizations
  - Coordinating Committee members selected
  - RAND contracted: screened >12,000 titles & reviewed >1200 articles (1/88 – 9/09)
  - 5 expert panels formed: *Definitions; Symptoms & Natural History; Diagnosis; Management; & Management of Food-induced Anaphylaxis*
- 3/2010 – 60 day pubic comment period
  - 550 received & reviewed; modified Guidelines
- 12/6/2010 National Guidelines released

NIAID Diagnostic Guidelines

- #2 – Recommends detailed medical history to focus evaluation & physical exam useful to identify signs of FA, but neither can be considered diagnostic
- #4 – Recommends SPT to assist in identification of potential IgE-mediated food allergens, but alone SPT cannot be considered diagnostic
- #5 – Recommends not using intradermal skin tests

NIAID Diagnostic Guidelines

- #7 – Recommends food-specific IgE to assist in identification of potential IgE-mediated food allergens, but alone cannot be considered diagnostic
- #8 – Suggests that the atopy patch test not be used for routine evaluation of non-contact food allergy
- #10 – Suggests that elimination diets may be useful identifying food allergens, especially in non-IgE allergy

NIAID Diagnostic Guidelines

- #11 – Recommends using oral food challenges:
  - DBPCFC is the "gold standard"
  - Single-blind & Open challenges "diagnostic" if challenge negative or they elicit objective symptoms correlating with medical history plus supportive lab data
- #12 – Recommends not using the following: BHR* assays; lymph stimulation, food-specific IgG or IgG4, cytotoxicity assays, etc.

DIAGNOSING FOOD ALLERGY

- *History:* ~ 30% - 40% confirmed
- *Specific IgE or Skin Tests :* ~30% - 40% confirmed
- *Elimination Diets:* 0% - 40% confirmed

DBPCFC is the "GOLD STANDARD"

- Single-blind & open challenges may be diagnostic
- Time consuming, costly & poorly reimbursed
- Stress on the patient including the risk for an anaphylactic reaction

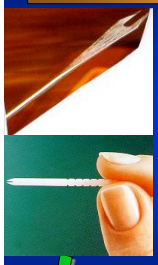
Tests for the Diagnosis of IgE-mediated Food Allergy

Correlation of the outcome of DBPCFC with

- food allergen-specific IgE concentrations in the serum; component-based assays
- Skin prick test wheal diameter

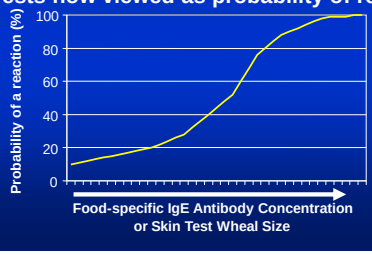
Development of diagnostic decision points that are 90% to 95% predictive of clinical reactivity

Prick Skin Testing



Paradigm Shift in Interpretation

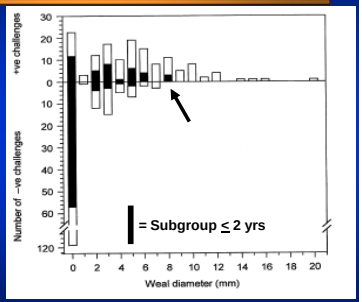
- Tests were viewed as positive or negative
  - e.g., a 3 mm wheal is a positive test
- Tests now viewed as probability of reaction



Predictive Value of PSTs

Comparison of PST results & outcome of oral milk challenges
- 120 challenges
- 37% positive

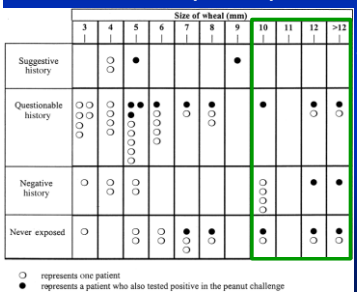
Wheal	>100% PPV
Milk	≥ 8 mm
Egg	≥ 7 mm
Peanut	≥ 8 mm



Sporik R et al. *Clin Exp Allergy*, 2000; 30:1541-46

PST Wheal Size & Reactivity

- 64 of 140 children evaluated for peanut allergy had a +PST
  - 18 of the 64 had positive peanut challenge



- Children with positive challenges had PSTs ≥ 5 mm
- 9 of 17 children with PST ≥ 10 mm had a negative challenge

Pucar et al. *Clin Exp Allergy* 2001; 31:40-46.

Features Affecting Skin Tests

- Extract – non-standardized; lot-to-lot variation
- Device used for prick/puncture
- Operator – pressure applied during application; precision of measurement
- Location of skin test – back > volar aspect of arm; mid- & upper- back > lower back; proximal forearm > distal forearm [3 cm/5 cm]
- Means of measuring wheal size
- No added value for intradermal testing

Bock et al. *JACI* 1978; 8:559-64

DIAGNOSING FOOD ALLERGY

- Development of *in-vitro* diagnostic tests for IgE-mediated food allergy

1. Predicting the outcome of oral challenge tests

   ⇩

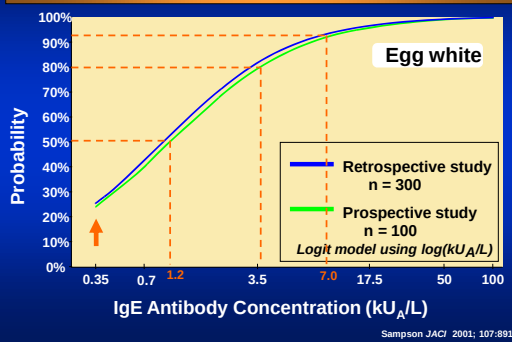
   Replacing oral food challenges

2. Predicting the long-term prognosis

   ⇩

   Selecting children for whom immunotherapy would be of benefit in the future

Probability of Reacting to Egg



Sampson *JACI* 2001; 107:891-96.

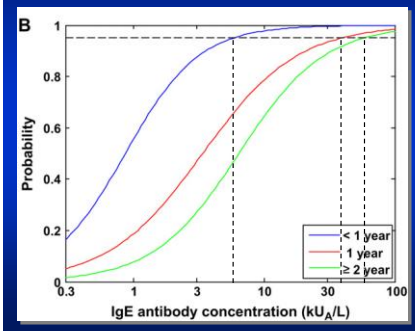
95% Predictive Decision Levels

Allergen	Decision Pt (kU_A/L)	PPV	Sens.	Spec.
Egg	7	98%	61%	98%
(≤ 2 yrs of age)+	2	95%		
Milk	15	95%	57%	94%
(≤ 1yr of age)++	5	95%		
Peanut	14	100%	57%	100%
Soy	30	73%	44%	94%
Wheat	26	74%	61%	92%
Tree nuts+++	15	95%	----	----

\+ Boyano MT, et al. *Clin Exp Allergy* 2001; 31:1464-9.
++ Garcia-Ara C, et al. *JACI* 2001; 107:185-90.
+++ Clark AT, Ewan P. *Clin Exp Allergy* 2003; 33:1041-45.
Maloney J et al. *JACI* 2008; 122:145-5.

Sampson *JACI* 2001; 107:891-96.

Age-related Probability of Reacting to Milk

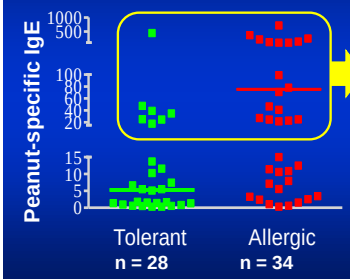


861 oral food challenges performed in 969 children age range: 0.2 – 14.6 yrs

Komata T et al. *JACI* 2007; 119:1272-74.

Peanut-specific IgE

• Challenged 62 children with suspected peanut allergy



25 patients with peanut-specific IgE > 15 kU_A/l

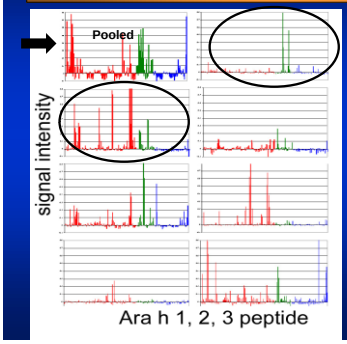
28% wrong diagnosis

Beyer et al. personal communication

Diagnostic Decision Points

- Variations by age and atopy status.
- Equivocal areas [20th to 80th percentile]
- Decreasing IgE levels with food avoidance
- Not established for many foods, e.g. cereal grains, shell fish or tree nuts.
- For several foods, e.g. wheat and soy, the PPV of the diagnostic decision point are <75%

Epitope Diversity & Reactivity



Greater epitope diversity = more peanut-specific IgE molecules present on mast cells ➔ greater releasibility

Greater epitope diversity = more severe reactions

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

Component Resolved Diagnostics in Food Allergy

	Pollen cross-reactive components*	LTP	Pollen non-cross-reactive components**
Peanut	Ara h 8 Ara h 5	Ara h 9	Ara h 1; Ara h 2; Ara h 3 Arah 4; Ara h 6; Ara h 7
Hazelnut	Cor a 1 Cor a 2	Cor a 8	Cor a 9 Cor a 11
Soybean	Gly m 4 Gly m 3	Gly m 1	Gly m 5 Gly m 6
Wheat	Tri a 12	Tri a 14	Tri a 19 (ω-5 gliadin) Tri a 21 - alfa gliadin Tri a 26 - HMW glutenin Tri a 28 - AAI dimer 0.19

PRP-10

Profilin

Ana risk

*Birch tree pollen, Timothy grass pollen for wheat
** Storage seed proteins, albumins and globulins

Component Resolved Diagostics in Food Allergy

- Ara h 2 > 1.63 kU_A/L → 123/123 positive challenge
  - Ara h 2 <1.63 kU_A/L → 52/82 positive challenge
  - Ara h 2 level does not predict threshold dose

  Bindslev-Jensen C. et al.
- Poor correlation between fruit & hazelnut IgE & reaction
- Sensitization to Bet v 1 homologues, Pru av 1/Mal d 1/ Cor a 1, is a risk factor for OAS
- Sensitization to LTPs, Pru av 3/Mal d 3/Cor a 8/Jug r 3, is a risk factor for systemic reactions to cherry/apple/ hazelnut/walnut (30% - 50%)
  - sensitization to Cor a 9 is a risk factor for systemic reaction, especially in children Beyer JACI 2002; 110:517.

Cross-reactivity in Testing

Food Allergy [cross-reactivity often > 80%]	Prevalence of Allergy to > 1 Food in Family
Fish	30 – 100%
Tree nut	15 – 40%
Grains [wheat, rye, barley, oat}	15%
Milk [cow, goat, sheep]	90%
Legumes [peanut, soy, pea, beans]	10%
Milk / Beef Egg / Chicken	10%

Quantitative IgE Measurement Over Time as Monitoring Parameter

- Studies support concept that IgE levels can be monitored to assist the physician in determining when it may be worthwhile rechallenging a patient with food allergy:
  - Egg < 1.5 kU/l
  - Milk < 7 kU/l
  - Peanut < 2 kU/l

Sampson, J Allergy Clin Immunol 2001
Skolnick et al, J Allergy Clin Immunol 2001
Sampson, Curr Opin Allergy Clin Immunol 2002

Summary: Diagnostics

- PSTs and allergen-specific IgE both may be useful in the diagnosis & management of IgE-mediated food allergy, but alone without collaborating history are never sufficient
- When interpreting results, must consider several factors:
  - predictive value of test result
  - strength of history
  - age of patient & potential cross-reactivities
- When considering OFC, consider benefit of adding food & probability of passing