

Cracking the Code: Modern Approaches to Food Allergy Diagnosis

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Disclosures

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Pfizer, Bausch Health, Covis, Trudell, Nutricia

Investigator: ALK, DBV, Dermavant, Astra-Zeneca

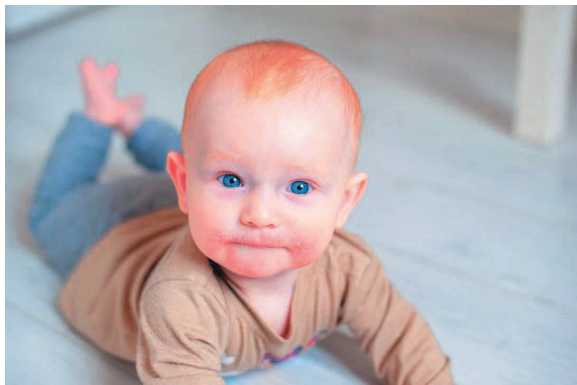
*The opinions reflected in this presentation are those of the speaker
and independent of Nutricia North America*

Learning Outcomes

By the end of this session, the learner should be able to:

1. Differentiate IgE and from non-IgE food allergies
2. Review appropriate selection and interpretation of food allergy tests for IgE and non-IgE food allergies
3. Considerations when conducting food challenges for diagnostic work up of food allergies

CASE: JACOB – 5 months



- 5-month-old boy with mild eczema
- Mother has peanut allergy
- Breastfed
- Beginning to introduce complementary food to reduce the risk of food allergy
- Starts with “just add water” rice cereal

CASE: JACOB – 5 months



- Within 5 minutes develops hives on face and abdomen
- 15 minutes later vomits and develops lethargy
- EMS called and epinephrine is administered.
- Is this anaphylaxis?
- Is this rice allergy?

CASE: JACOB – 6 months



- Has been referred to pediatric allergist
- At the allergy appointment mom wonders whether “just to test for everything just in case?”
- She also asks “Does the allergy cause eczema?”

	IgE-mediated CMPA		Non-IgE-mediated CMPA
Reaction Type	Acute		Non-Acute
Rapidity of Symptom Development	Minutes to hours		Several hours to several days
Typical Age of Presentation	After several months of life		After a few days or weeks of life
GI Symptoms	<ul style="list-style-type: none"> • Abdominal pain • Vomiting • Diarrhea 		Upper GI: - DELAYED Vomiting (if repetitive can lead to hypotension) - Severe reflux - Irritability Middle GI: - Abdominal cramping - Abnormal bowel movement - Failure to thrive Lower GI: - Mucus and/or blood in stools
Skin-related Symptoms	<ul style="list-style-type: none"> • Urticaria • Angioedema 	• Pruritus	Rare
Respiratory Symptoms	<ul style="list-style-type: none"> • Cough • Wheezing • Acute rhino-conjunctivitis • Respiratory distress/Dyspnea 		None
Systemic Symptoms	• Hypotension	• Lethargy	Hypotension, lethargy possible
Possible Disorders	Anaphylaxis		<ul style="list-style-type: none"> • Esophagitis • Gastritis • FPIES • Enterocolitis • Proctocolitis

Adapted from table developed by Dr. Marie-Josée Francoeur, Dr. Reza Alizadehfard, Dr. Valérie Marchand, and Dr. Saul Greenberg.



DIAGNOSIS OF FOOD ALLERGIES





HISTORY!!!

HOW DO WE DIAGNOSE FOOD ALLERGY?

Non-IgE-mediated CMPA



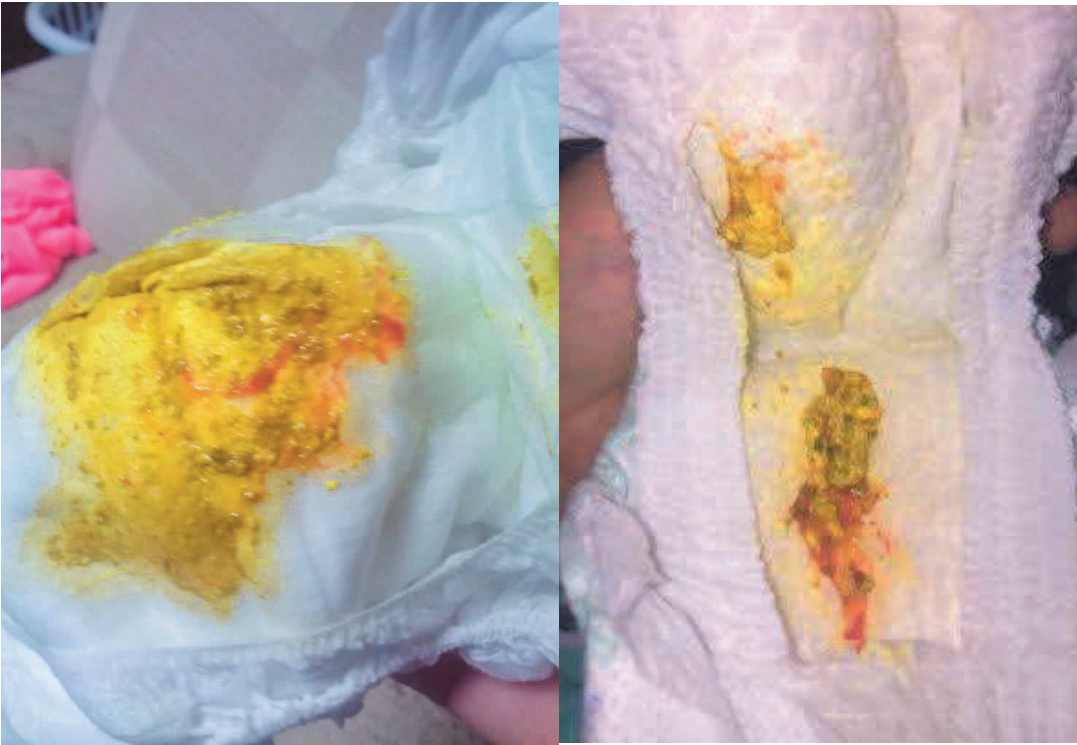
Usually appears:

- In **first few weeks of life before 6 months** of age
- In **breastfed children whose mothers consume cow's milk**, or **infants given formulas** containing cow's milk protein or soy
- **Several hours to several days** after consumption

Presentation:

- GI symptoms include **diarrhea, mucus in stools and rectal bleeding**
- GI disorders range from **esophagitis to gastritis, gastroenteritis and colitis**
- Symptoms of esophagitis **resemble gastroesophageal reflux**
- **Delayed onset vomiting**

There are no reliable tests for non-IgE-mediated CMPA



Diagnosis

Diagnosis

Elimination of CMP and re-challenge

Breastfed infants

- Encourage mother to **continue breastfeeding**
- If desired, mother can eliminate all milk and dairy products from her diet **for up to 14 days**
- If symptoms improve: **Re-introduce CMP** and dairy products to the mother's diet to confirm that it elicits the same symptoms
- A positive response can be diagnostic; mothers who wish to continue breastfeeding should receive **nutritional counselling** to achieve exclusion of milk and dairy products from their diet and consider calcium supplements



Diagnosis

Elimination of CMP and re-challenge

Non-breastfed infants

- Eliminate cow's milk formula and any foods containing milk protein from the infant's diet
- Elimination diet begins with introduction of an extensively-hydrolyzed or amino-acid based formula



Koletzko S, et al. J Ped Gastroenterol Nutr. 2012;55(2):221-229.

Infant Formulas: Protein Structures

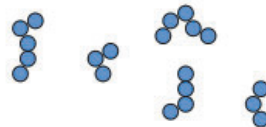
Intact:



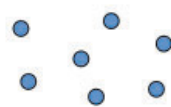
Partially Hydrolyzed:



Extensively Hydrolyzed:



Amino Acid:



Eczema is not Food IgE-mediated!



Therefore, testing is not indicated or relevant!!!

CASE: JACOB – 6 months



- Clearly, based on history, Jacob does not have non-IgE mediated food allergy

IgE-Mediated Food Allergy

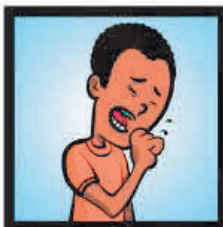
- Food allergy is (typically) not part-time
- Symptoms are typically rapid onset and short lived
- Often on first few exposures
- A detailed evaluation of the ingestion of food including ingredient list is key
- Chronic urticaria and eczema are not food allergy

Food Allergy Symptoms

A severe, life-threatening allergic reaction, is called ***anaphylaxis***



Skin: Widespread hives, swelling, itching, warmth, redness



Breathing: Coughing, wheezing, shortness of breath, chest pain/tightness, throat tightness, hoarse voice, trouble swallowing



Heart: Pale or blue colour, weak pulse, dizzy or lightheaded



Stomach: Nausea, pain, cramps, vomiting

Useful questions for the medical history

Was one of the most common allergens ingested within 2 hours prior to the reaction?

- Most allergies caused by cow milk, eggs, peanuts, tree nuts, shellfish, finned fish, wheat and soy

Did the patient previously ingest the suspect food?

- Having a consistent history of eating the food suggests it is less likely the culprit

Have there been previous reactions?

- Multiple reactions increases likelihood that the suspected food is the culprit

What was the age of onset

- Onset in childhood: most likely milk, egg, wheat or peanut allergy
- Onset in adulthood: usually due to nut or shellfish allergy or pollen allergy syndrome

How was the food prepared

- Larger amounts of food increases likelihood of a reaction
- Patients allergic to whole cow milk may tolerate it in a baked form

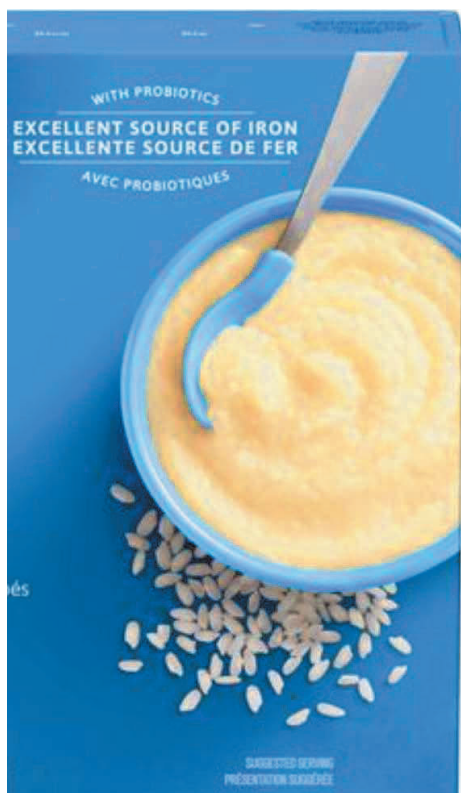
Did any factor augment the intensity of the allergy?

- Exercise, infection, medications, menstruation, and alcohol may increase likelihood of a reaction or make it more severe if a reaction does occur

What were the symptoms of the allergy

- Cutaneous, respiratory, GI, CV – indicative of IgE-mediated reaction
- Older individuals may respond with as sense of doom
- Younger individuals may cry, stop playing or become restless

Adapted from Abrams et al, CMAJ, 2016



INGREDIENTS: RICE FLOUR[†], DRY SKIM MILK[†], CANOLA OIL[†], HIGH OLEIC SUNFLOWER OIL[†], SUNFLOWER OIL[†], BIFIDOBACTERIUM LACTIS[†].

VITAMINS AND IRON: THIAMINE MONONITRATE[†], RIBOFLAVIN[†], NIACINAMIDE[†], FERRIC PYROPHOSPHATE[†].
CONTAINS MILK. MAY CONTAIN WHEAT, BARLEY, AND OAT.

INGRÉDIENTS: FARINE DE RIZ[†], LAIT ÉCRÉMÉ EN POUDRE[†], HUILE DE CANOLA[†], HUILE DE TOURNESOL À HAUTE TENEUR EN ACIDE OLÉIQUE[†], HUILE DE TOURNESOL[†], BIFIDOBACTERIUM LACTIS[†].
VITAMINES ET FER: MONONITRATE DE THIAMINE[†], RIBOFLAVINE[†], NIACINAMIDE[†], PYROPHOSPHATE FERRIQUE[†].
CONTIENT DU LAIT. PEUT CONTENIR DU BLÉ, DE L'ORGE ET DE L'AVOINE.

GOLD STANDARD:
**Oral Food
Challenge**



DIAGNOSIS OF FOOD ALLERGIES

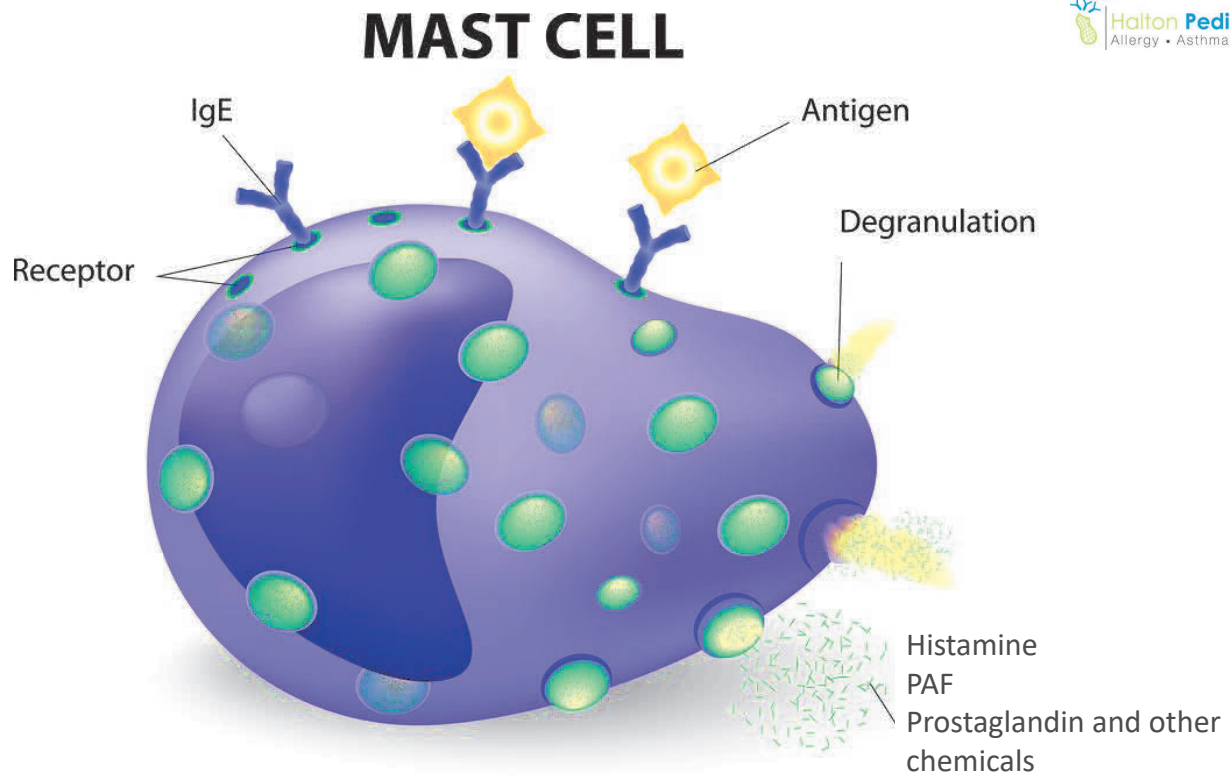


Pediatric allergist confirms IgE-mediated food allergy diagnosis:

- **A thorough review** of the history
- **Skin prick testing**
- **Evaluation** of serum-food-specific IgE
- **Formal oral food challenges** performed in a supervised setting



© 2014, The FPIES Foundation



**GOLD
STANDARD:
Oral Food
Challenge**



IN-VITRO DIAGNOSIS OF FOOD ALLERGIES

1st
Generation

- Skin prick Test

2nd
Generation

- Serum IgE to foods

3rd
Generation

- Component Resolved Diagnostics

4th
Generation

- Microarray
- Basophil Activation

Canadian Society of Allergy and Clinical Immunology position statement: panel testing for food allergies



Abdulrahman Al Ghamdi^{1,2}, Elissa M. Abrams^{3,4}, Stuart Carr⁵, Mariam A. Hanna⁶, Sari M. Herman⁷, Elana Lavine⁸, Harold Kim^{9,10}, Timothy K. Vander Leek^{11,12} and Douglas P. Mack^{13,14*}

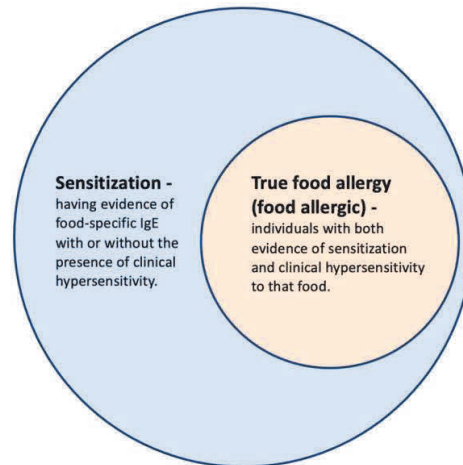


Fig. 1 Sensitization versus True Food Allergy

Al Ghamdi, A et al, AACI, 2024

**Perform
diagnostic
test**



Greenhawt MJ, et al. J Allergy Clin Immunol. 2020;146:1302-1334.

Skin Prick Tests

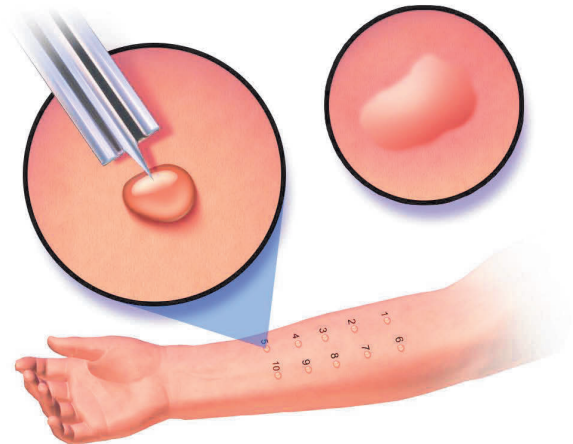
Allergen solution is placed on the skin

Positive test:

- Skin is red and itchy

Negative test:

- No reaction



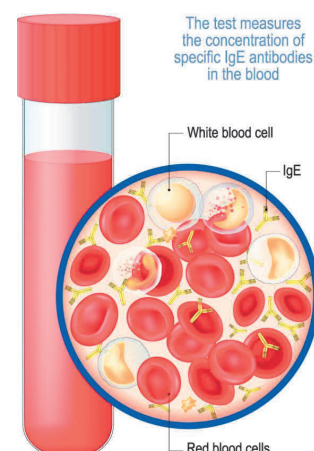
©BruceBlaus, CC by-sa 4.0

Serum IgE

An allergy blood test

Blood test measures levels of allergy antibody or IgE

Blood is mixed with a series of allergen in a laboratory



Often referenced, poorly validated

Likelihood Indicators for Positive or Negative OFC in Children

Food	Serum Food-IgE (kIU/L)		SPT wheel (mm)	
	~95% Positive	~50% Negative	~95% Positive	~50% Negative
Cow milk	≥ 15 ≥ 5 if younger than 1 year	≤ 2	≥ 8	
Egg white	≥ 7 ≥ 2 if younger than 2 years	≤ 2	≥ 7	≤ 3
Peanut	≥ 14			
Fish	≥ 20	≤ 2 with and ≤ 5 without history of peanut reaction	≥ 8	≤ 3

Adapted from Nowak-Węgrzyn et al. J Allergy Clin Immunol 2009;123:S365-83.

Component Resolved Diagnostics

Allergen Sources have many
allergenic and non-allergenic
molecules



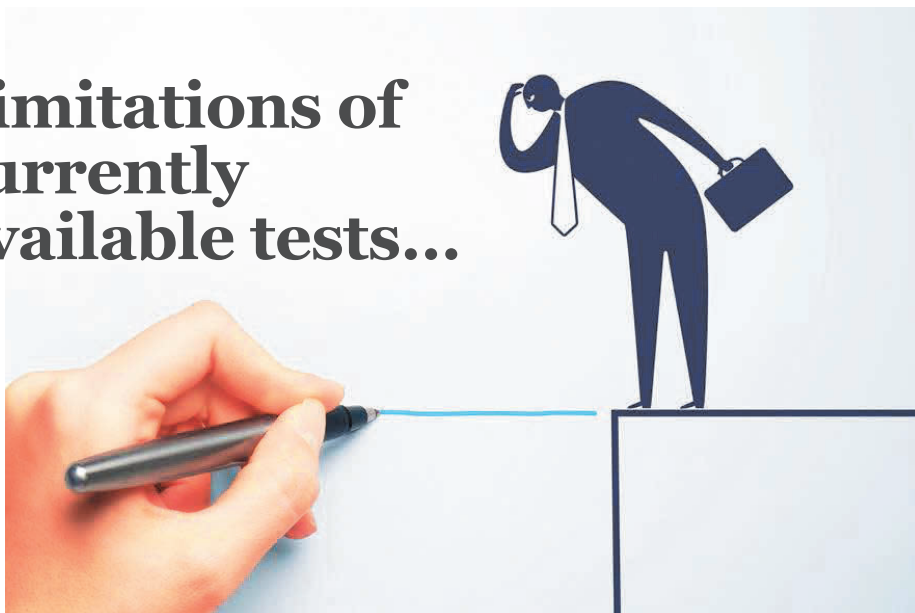
Microarray Testing

- Small volume sample
- Specific IgE against numerous target proteins
- Allergen components + whole allergen extracts can be immobilized on microarrays
- Runs the risk of non-specificity and overdiagnosis



MICROARRAYS = Component Resolved Diagnostics + Serum IgE

Limitations of currently available tests...



- ✓ **Detect** sensitization
- ✓ **Cannot** detect clinical allergy
- ✓ **Cannot** predict severity
- ✓ **Cannot** predict prognosis

Basophil Activation Testing

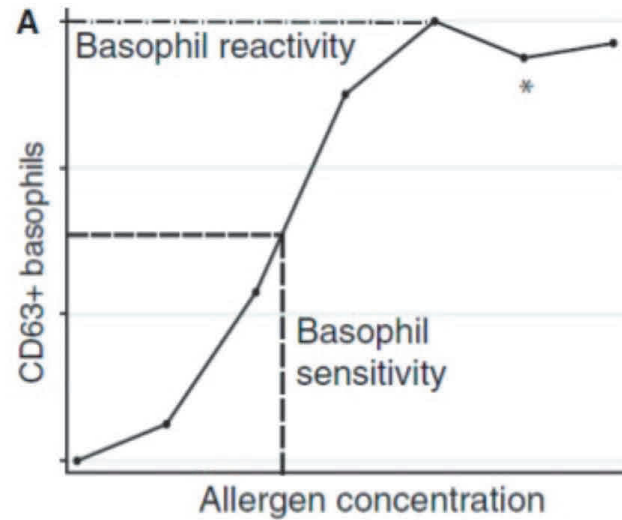
Less stressful for the patient

Avoids severe reactions

NOT readily available

Basophil REACTIVITY can reflect severity

Basophil SENSITIVITY can suggest threshold of response to allergen



Hoffmann et al. 2017;41(4):159-66.



PLEASE HELP ME STOP THE INSANITY!

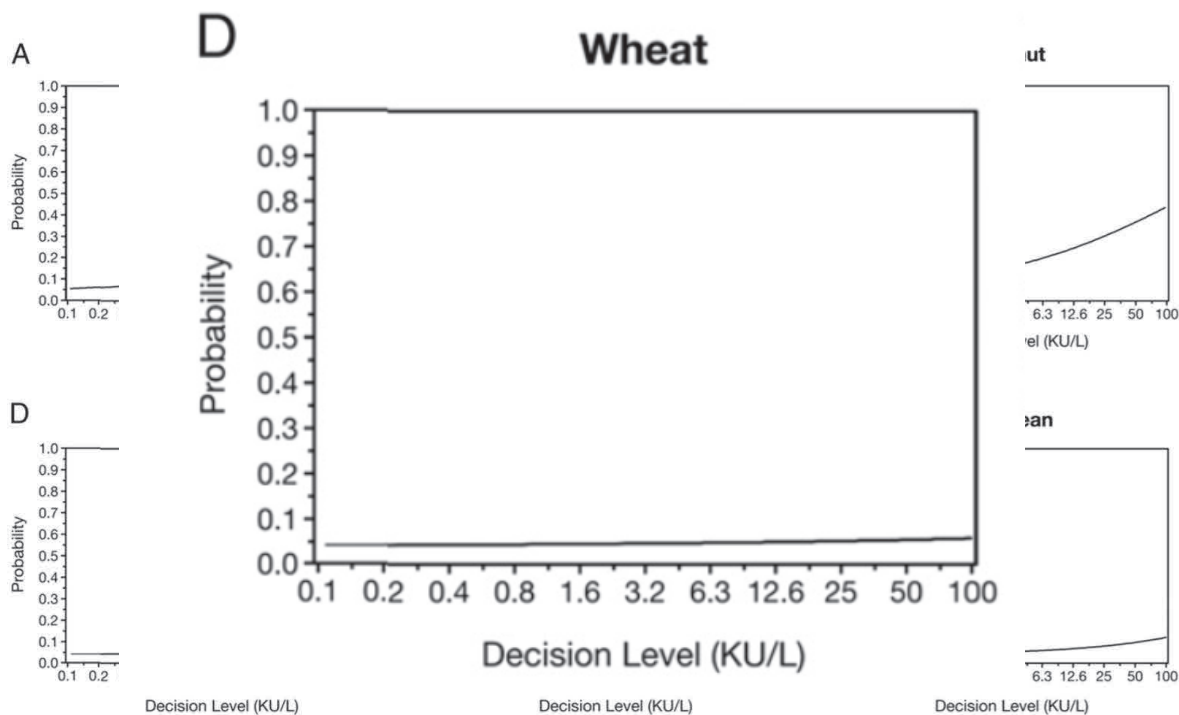
Food Allergy in Infants With Atopic Dermatitis: Limitations of Food-Specific IgE Measurements

PEDIATRICS Volume 136, number 6, December 2015

Jonathan M. Spergel, MD, PhD^a, Mark Boguniewicz, MD^b, Lynda Schneider, MD^c, Jon M. Hanifin, MD^d, Amy S. Paller, MD^e, Lawrence F. Eichenfield, MD^f

“...results of this study of food allergy development in >1000 infants with AD **do not support the use of sIgE testing** for these infants **as a diagnostic substitute for food challenge** and should discourage pediatricians from prescribing food elimination diets on the basis of sIgE levels alone.”

Spergel et al, Pediatrics, 2015



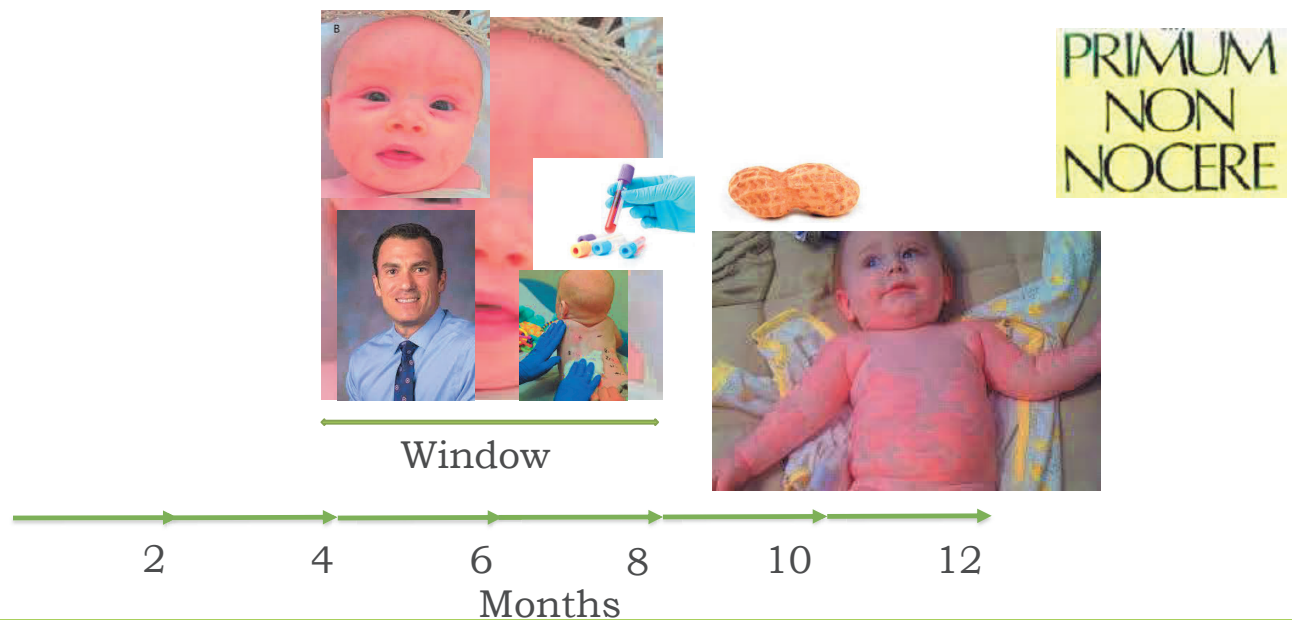
Spergel et al, Pediatrics, 2015

Table II. OFC results on foods avoided due to immunoassay or PST

Food group	Avoiding on admission	OFC positive result	OFC negative result	Avoiding on discharge	% Negative
Egg	10	1	9	1	90%
Fruits	10	2*	8	2	80%
Meats	13	0	13	0	100%
Milk	9	0	9	0	100%
Oats	4	0	4	0	100%
Peanut	7	1	6	1	86%
Shellfish	2	0	2	0	100%
Soy	19	1	18	1	95%
Vegetables	6	0	6	0	100%
Wheat	13	3	10	3	77%
Other	18	0	18	0	100%
Totals	111	8	103	8	93%

Spergel et al, Pediatrics, 2015

What's the harm?



Canadian Society of Allergy and Clinical Immunology position statement: panel testing for food allergies

Abdulrahman Al Ghamdi^{1,2}, Elissa M. Abrams^{3,4}, Stuart Carr⁵, Mariam A. Hanna⁶, Sari M. Herman⁷, Elana Lavine⁸, Harold Kim^{9,10}, Timothy K. Vander Leek^{11,12} and Douglas P. Mack^{13,14*}

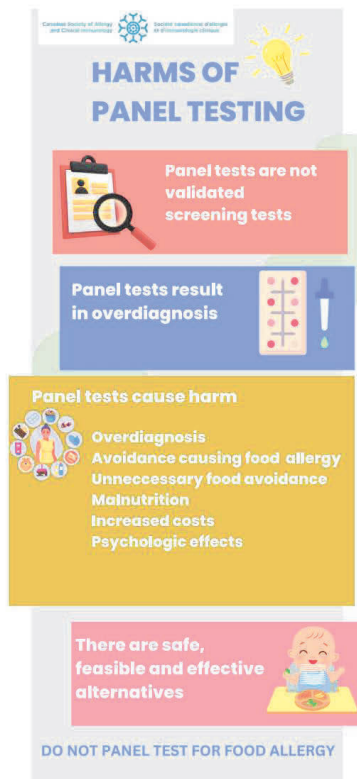


Fig. 2 Infographic for patient and clinician education regarding the harms of panel food testing

Al Ghamdi, A et al, AACI, 2024

CASE: JACOB – 24 months



- Baked goods were introduced but family didn't feel comfortable with full ladder
- Repeat skin testing was 2 mm and OFC confirmed tolerance of milk

Oral Food Challenges



What research on almond OFCs tells us

Challenge Fail Rates by Almond SPT (A) and Almond Specific IgE (B)

A. SPT Size (mm)	N (%)	Failed challenge	Grade 2/3 Reaction	Anaphylactic reaction
0-2	203 (34)	3%	0.5%	0%
3-4	122 (21)	3%	2%	0%
5-6	124 (21)	7%	6%	1%
7-8	60 (10)	10%	5%	2%
>8	61 (10)	10%	10%	2%
B. Specific IgE level	N (%)	Failed challenge	Grade 2/3 Reaction	Anaphylactic reaction
<0.35	195 (33)	3%	0.5%	0%
0.35-1.00	109 (18)	3%	3%	0%
1.01-2.00	86 (15)	12%	9%	1%
2.01-10.00	136 (23)	3%	2%	0%
>10.00	44 (7)	17%	14%	5%

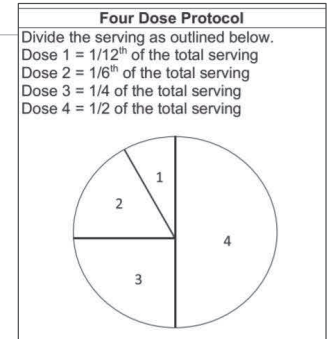
More than 90% passed

Rates of not passing much lower than other nuts

When reactions occur, they are mostly mild

How does the OFC work?

- Typically 2-5 hours
- Parents typically bring in food in various forms (should be palatable!)
- Initial assessment
- Food divided into increasing doses and given every 15-30 minutes
- Observation time of 1-2 hours
- Routine ingestion recommended after



Age-Specific Serving Size for Open OFC

Allergen	Food	Protein content/serving	4 – 11 mo	1-3 y	4-8 y	9-18 y	19+y
Peanut	Peanut (whole)	2 g/ ~8 peanuts					
	Peanut butter	3 g/1 tbsp	1 rounded tbsp	1-2 tbsp	1-2 tbsp	2 tbsp	2 tbsp
	Peanut flour or peanut butter flour	3 g/1 tbsp original or 2.25 g/1 tbsp chocolate flavour	1 rounded tbsp	1-2 tbsp	1-2 tbsp	2 tbsp	2 tbsp
	Peanut/chocolate candy cups (full size)	0.875 g/1 cup		1-2 candy cups	1-2 candy cups	2-3 candy cups	2-3 candy cups

Bird et al, JACIP, 2020

Reactions

- Severe reactions rare
- Often skin or gastrointestinal
- Reactions often treated with antihistamines, albuterol
- Epinephrine use is possible



Epinephrine treatment is infrequent and biphasic reactions are rare in food-induced reactions during oral food challenges in children

- Of 1273 OFCs, only 34% reacted
- Only 3.9% required epinephrine (11% of those who reacted)
- Only 3 require 2 doses of epinephrine
- 1 biphasic reaction

Jarvinen et al, JACI, 2009

When do we consider an Oral Challenge

- “Serum IgE testing and/or skin prick test (SPT) results are not consistent with the patient history.
- When the family/patient and physician agree that the risk estimated from the medical history and the test results is outweighed by the benefit of possibly adding a food to the diet.
- Expanding the diet in persons with multiple dietary restrictions.
- Assessing the status of tolerance to cross-reactive foods.”
- Also... Prior to considering a treatment like OIT or SLIT



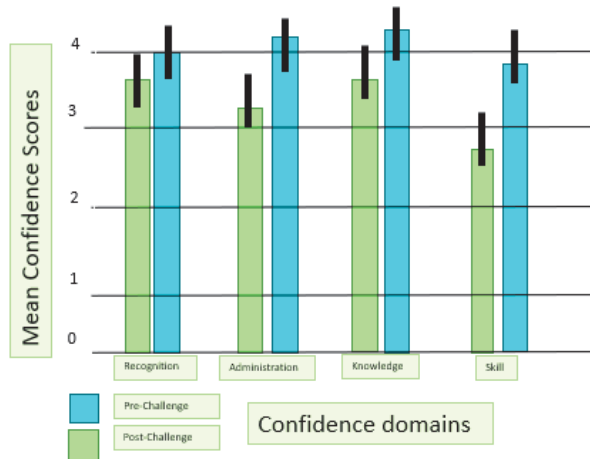
Bird et al, JACIP, 2020

The benefits of oral food challenge

Clinical Communications

The impact of tree nut oral food challenges on quality of life and acute reactions in nut allergic patients

Jennifer A. Dantzer, MD, and Robert A. Wood, MD

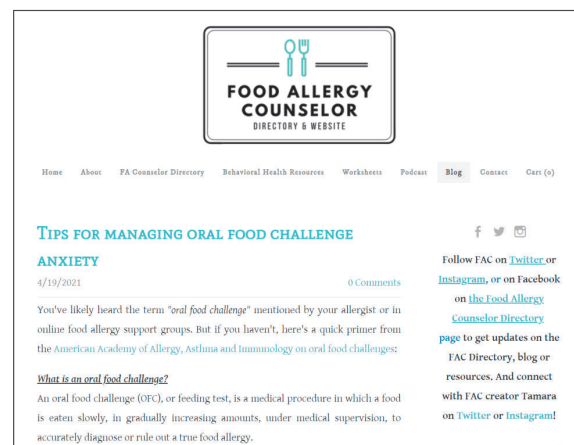


Dantzer and Wood, JACIP, 2019; Soller et al, JACIP 2019

Cautions and Hesitations

Why should you reschedule or delay an OFC

- Ongoing illness, fever, or active respiratory symptoms (like wheeze or cough)
- Utilized a short-acting β -agonist in the previous 48 hours for symptoms of cough or wheeze
- Poorly controlled asthma, AD, or allergic rhinitis
- Unstable cardiovascular disease
- Beta-blocker therapy
- Patient has not discontinued medications e.g. antihistamines, benzodiazepines, antidepressants, beta-blockers etc...



Bird et al, JACIP, 2020

In this seminar we have discussed

- ▶ History is key to diagnosis
- ▶ Diagnostic tests augment allergy diagnosis
- ▶ Oral challenges are the Gold Standard for the diagnosis of food allergy and challenges are safe and even when a reaction occurs there can be benefit
- ▶ Panel testing is not recommended

Questions? Thank you!

