

LABORATORY MONITORING & OUTCOME PREDICTIONS

ATUL N. SHAH, MD, FACAAI, FAAAAI NEW YORK FOOD ALLERGY

What We Want To Know

Johnny - 4 yr old, starting Peanut OIT



Outcomes - desensitization, sustained unresponsiveness, tolerance

- What tests?
- How often?

to

- Predict outcomes
- Predict potential issues





2022 FAST Survey

Q8: How often do you monitor labs while the patient is on maintenance OIT?



2022 FAST Survey

Q9: What test(s) do you typically check during maintenance OIT? (check all that apply)



Scope of Discussion

- Pre-procedure testing
- Monitoring tests
- Frequency of testing
- Response to test results
- Costs of testing
- Outcome Prediction with each tests
- Clinical Observations
- Experience

Scope of Discussion

- Pre-procedure testing
- Monitoring tests
- Frequency of testing
- Response to test results
- Costs of testing
- Outcome Prediction with each tests
- Clinical Observations
- Experience

- Skin Tests
- CBC with Diff
- slgE, Total lgE
- Components IgE
- IgG4
- Vitamin D Level
- BAT, MAT
- Epitope testing
- CD8+T-cells
 - EoP

Skin Tests

PPOIT trial -

There was a significant longitudinal reduction in median peanut SPT and Ara h 2 slgE along with an increase in median slgG4 to peanut and Ara h 1,2,3 in children who achieved SU in PPOIT trial.

> **915** Predicting Acquisition of Sustained Unresponsiveness Following Peanut Oral Immunotherapy Using Skin Prick Test Size and Serum Levels of Immunoglobulins Specific to Peanut

> Lalita Jindal^{1,2}, Anne-Louise Ponsonby, PhD^{3,4}, Paul Licciardi, PhD^{4,5},

CBC - with Differential

- WBC, Hb, Platelets
- Peripheral Eosinophils (pEos) baseline
- EoE (no relation to pEos)
- ELORS (elevation in pEos)
- Needed with BAT, EoP and SIP to identify peripheral Basophils, Eosinophil Progenitor Cells and total Lymphocytes

2022 FAST - No OIT Data

sIgE / Total IgE Ratio.,

Does this ratio improve prediction of OFC outcome?

Some studies ++ and some studies -- (no change vs slgE alone)

- Discrepancy due to to the foods studied
 - Gupta et al -- useful for persistent food allergies eg, peanut, tree nuts, shellfish, and seeds
 - Mehl et al -- evaluated foods that often have transient allergy, cow's milk, egg, and wheat

- A multicenter study of children with suspected PN or hazelnut allergies evaluated Ara h2, PN, and hazelnut IgE ratios (Grabenhenrich L. et al. JACI 2016)
 - Peanut-specific/total IgE was also not better than Ara h 2 sIgE in diagnosing PA
 - Similar results were reported for hazelnut allergy

2022 FAST - OIT

sIgG4 / sIGE Ratio

Does this ratio improve prediction of OFC outcome?

- Diagnostic utility has not been established
- Sensitized/tolerant children tend to have higher allergen-specific IgG4/IgE ratios than allergic children
 - Higher ratio in children who do not knowingly eat peanut
 - Increases over time in patients undergoing OIT and other forms of food immunotherapy

Food slgE, lgG4, Components

Lancet -

Association with SU When Pre-OIT values:

- Higher baseline peanut-specific IgG4/IgE
- Lower Ara h 2 lgE
- Lower basophil activation responses

Sustained Outcomes in a Large Double-blind, Placebo-controlled, Randomized Phase 2 Study of Peanut Immunotherapy. R. Sharon Chinthrajah, MD... Lancet. 2019 October 19; 394(10207): 1437–1449. doi:10.1016/S0140-6736(19)31793-3.

slgE - CRD

 CRD - Component-Resolved Diagnostics measures IgE binding to specific molecular proteins in an allergen, instead of sIgE just for allergen

Qs from 2022 FAST meeting

• Has anyone found CRD during maintenance to be helpful in addition to just slgE? Is BAT during maintenance predictive or helpful?

slgE - CRD - Total IgE

		· · · · · · · · · · · · · · · · · · ·						
New York Food	d Allergy & Well	ness						
ATUL N. SHAH	H, MD, FACAAI,	FAAAAI						
NYFoodAllergy	.com	631-446-1436						
OIT	Food	Day 1 Date	Challenge	Daily Dose		Infancy		
1	Milk	09/08/2020	3/2/2021	240mL		Atopic March		
2								
3								
Food	Components	11/11/2016	04/28/2017	07/21/2020	04/02/2021	07/08/2021	12/18/2021	06/08/2022
				Pre-OIT	POST-OIT			
Total IgE		1612	1443	915	1194	967	1075	1577
Vit D 250H		14.7	14.7	37	42.1	39	39.3	40.2
AEC								
Milk	SPT							
	slgE	87	>100	>100	42	26.3	21.3	13.4
	Alpha-Lactalbu	0.7	39.8	12.4	8.29	4.95	4.46	3.12
	Beta-Lactoglob	8.96	50.8	7.82	3.19	2.25	2.1	1.46
	CASEIN*	>100	>100	>100	43.7	24.9	23.4	11.8
Birch	slgE / SPT	<0.10	1.32		0.81			52.3

Observation - Peanut

F001-IgE Egg White	<0.10	OBSERVATION	2 Months	RESULT
F013-IgE Peanut	<mark> </mark> >100	F013-IgE Peanut	Post PN-OIT	 38.20
Panel 603847 Show test details		Panel 603847 Sh	ow test details	
OBSERVATION	RESULT	OBSERVATION		RESULT
F422-IgE Ara h 1	<mark> </mark> 90.70	F422-IgE Ara h 1		 11.00
F423-IgE Ara h 2	<mark> </mark> >100	F423-IgE Ara h 2		9 33.40
F424-IgE Ara h 3	 58.70	F424-IgE Ara h 3		0 15.90
F352-IgE Ara h 8	<mark>e</mark> 2.19	F352-IgE Ara h 8		<0.10
		F427-IgE Ara h 9		<0.10

Role of PN Ara h 6 & BAT

- Patient seen for a second opinion
- No prior PN exposure
- OFC at a local academic institute as prior testing had low Ara h 2
- OFC Needed Epi
- Labs Ara h 6 High
- BAT reactive to PN

OBSERVATION		RESULT	REFERENCE / UoM
F013-IgE Peanut		<u> </u>	Class V kU/L
			Abnormal (app
Panel 604845	Show test details		
OBSERVATION		RESULT	REFERENCE / UoM
F422-IgE Ara h 1		0.61	Class II kU/L
			Abnormal (app
F423-IgE Ara h 2		0.13	Class 0/I kU/L
			Abnormal (app
F424-IgE Ara h 3		0.22	Class 0/I kU/L
			Abnormal (app
F447-IgE Ara h 6		 27.00	Class V kU/L
			Abnormal (app
F352-IgE Ara h 8		<0.10	Class 0 kU/L
F427-IgE Ara h 9		<0.10	Class 0 kU/L

Role of BAT - NYAIRL



CRD - Components List

- 1. Peanut
- 2. Brazil Nut
- 3. Walnut
- 4. Hazelnut
- 5. Cashew
- 6. Pistachio
- 7. Pecan
- 8. Milk
- 9. Eggs
- 10. Soy
- 11. Wheat
- 12. Sesame

- Ara h 2, 6, (1, 3, 9, 8)
- ► Bere1
- ▶ Jug r 1, (3)
- ▶ Cor a 9, 14, (1, 8)
- Ana o 3
- ► Cashew
- Walnut
- Casein, (ALA, BLG)
- Ovomucoid, (OA)
- nGly m 5, (6, 4)
- ▶ rTri a 19 Omega-5 Gliadin
- Sesi1

Monitoring Components

- Patients with High total IgE (AD, AR)
- slgE may not drop much during maintenance when total lgE stays high
- Reduction in components is helpful
- Ara h2 and Ara h 6 drops while Ara h 8 is high
- Maintenance Dose Reduction
- BAT association

Observation - Vit D levels (N=30-100, Target 50)

Recommend

Bringing the Next Generation of Food Allergy Diagnostics Into the Clinic

Alexandra F. Santos, MD, PhD^{a,b,c,d}, Michael D. Kulis, PhD^e, and Hugh A. Sampson, MD^f London, United Kingdom; Chapel Hill, NC, and New York, NY

Diagnostic test	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Epitope testing				
Bead-based epitope assay peanut ¹¹	92%	94%	91%	95%
Basophil activation test				
To peanut ^{12,13}	83% to 98%	96% to 100%	95% to 100%	83% to 98%
To cow's milk ¹⁴	91%	90%	81%	96%
To egg ¹⁵	90%	100%	100%	92%
Mast cell activation test to peanut ¹⁶	75%	99%	95%	92%

TABLE I. Diagnostic performance of next-generation food allergy diagnostic tests



Epitopes

EPITOPE MAPPING



Epitope Assay (BBEA)



2022 FAST

Epitope Testing: Pros / Cons of APD

- High Spec, Sens, PPV and NPV
 - Provides a probability that a patient can tolerate specific amounts of PN
 - Results can be superimposed with OIT dosing schedule / Palforzia ladder
 - Information will evolve with continued research and data
 - Applicable to peanut cultivars world-wide
 - Accessible due to mobile phlebotomy service

- Does not predict the severity of reaction
- May result in a false negative if no serum IgE is detectable, but this is validated in LEAP PN tolerant as well to low IGE threshholds
- Not recommended for patients on omalizumab or OIT currently
- Requires phlebotomy

Epitope Assay - PN OIT

Baseline Epitope Profiles are Predictive of Sustained High Threshold in the POISED Trial

Using epitope profiles to predict sustained unresponsiveness of peanut OIT.

Epitopes are 81% predictive

Abstract at AAAAI 2023: Mt. Sinai School of Medicine, Ashley San Eun Lee

Epitope Assay - Milk OIT

Predicting development of "sustained unresponsiveness" (SU) to milk oral immunotherapy using epitope-specific antibody binding profiles



BCT - Bandomized Controlled Trial

SU - "Sustained Unresponsiveness"

26

Epitope Assay - Milk OIT

Milk OIT:

- Those with SU exhibited less antibody binding to epitopes at baseline
- Using pre-OIT epitope-specific antibody binding a predictive model of SU can be built

Predicting development of sustained unresponsiveness to milk oral immunotherapy using epitope-specific antibody binding profiles

Check for updates

Mayte Suárez-Fariñas, PhD,^{a,b} Maria Suprun, MPH,^{a,c} Helena L. Chang, MS,^a Gustavo Gimenez, BS,^c Galina Grishina, MS,^c Robert Getts, PhD,^d Kari Nadeau, MD,^e Robert A. Wood, MD,^f and Hugh A. Sampson, MD^c New York, NY, Hatfield, Pa, Stanford, Calif, and Baltimore, Md

BAT- MAT







EDITORIAL

BAT- OIT

Basophil activation test: A diagnostic, predictive and monitoring assay for allergen immunotherapy

KEEPING TRACK OF PATIENTS ON ALLERGEN IMMUNOTHERAPY



Recommend

Early decrease in basophil sensitivity to Ara h 2 precedes sustained unresponsiveness after peanut oral immunotherapy



Sarita U. Patil, MD,^{a,b,c,d} Johanna Steinbrecher, BS,^a Agustin Calatroni, MS,^e Neal Smith, MS,^a Alex Ma, BS,^a Bert Ruiter, PhD,^{a,b,c,d} Yamini Virkud, MD, MPH,^{a,b,d} Michael Schneider, BS,^f and Wayne G. Shreffler, MD, PhD^{a,b,c,d} Boston, Mass, Chapel Hill, NC, and Schönenbuch, Switzerland

PN BAT with OIT

- Basophil sensitivity is a useful biomarker of sustained clinical efficacy after peanut OIT.
- With SU, basophil sensitivity was suppressed during BAT. The change from baseline to 3 months on OIT, was significantly greater in SU than in those with TDS
- TDS failed to change their basophil sensitivity, either early or later in OIT, had a significant rebound in their basophil reactivity AUC values.

Early decrease in basophil sensitivity to Ara h 2 precedes sustained unresponsiveness after peanut oral immunotherapy. Sarita U. Patil, MD... J Allergy Clin Immunol. 2019 Nov; 144(5): 1310–1319.e4.

BAT - PN OIT



Early decrease in basophil sensitivity to Ara h 2 precedes sustained unresponsiveness in peanut oral immunotherapy



PN BAT OIT

BAT at 3 months of OIT is a useful biomarker of sustained clinical efficacy after peanut OIT.

BAT to Ara h 2 has 2 potential uses during OIT

- early biomarker to identify those likely to have SU
- a marker after OIT to evaluate when clinical reactivity to peanut might be likely to return.

Early decrease in basophil sensitivity to Ara h 2 precedes sustained unresponsiveness after peanut oral immunotherapy. Sarita U. Patil, MD... J Allergy Clin Immunol. 2019 Nov; 144(5): 1310–1319.e4.

BAT- PN OIT

Lower basophil activation and peanut-specific IgE are associated with better outcomes after peanut oral immunotherapy



PN BAT OIT

- Peanut OIT suppresses basophil activation
- BAT can help to differentiate those who will achieve TDS from those who will achieve SU and tolerance after peanut OIT.
- Basophil non/low responders exhibit higher treatment success to peanut OIT
- 80% to 90% suppression of peanut-specific basophil activation is required to maintain long-term clinical tolerance after peanut OIT.

Sustained successful peanut oral immunotherapy associated with low basophil activation and peanut-specific IgE. Mindy Tsai... JACI 2020 Mar;145(3):885-896.e6

PN BAT - NYAIRL



BAT - Post OIT - NYAIRL

Antigen	Peanuts Sesame		ľ	analyze uale	3/28/202	2		
Physician	Atul Shah MD		F	Release date	3/29/202	2 8:48	РМ	
Accession Number								
K								
<u>LYM</u>	PHOCYTE AND BASOF	PHIL PHE	NOTY	PE RESULTS				
	% basoph	nils of WB	С					
Antigen 1:Peanut								
Basophil Phenotype	e 10,000 ng/ml	1.7	н	<1	1.16	н	<1.1	
Basophil Phenotype	e 1000 ng/ml	1.0		<1	1.61	н	<1.1	
Basophil Phenotype	e 100 ng/ml	4.5	н	<1	2.54	н	<1.1	
Basophil Phenotype	e 10 ng/ml	2.1	н	<1	2.66	н	<1.1	
Basophil Phenotype	e 1 ng/ml	0.6		<1	1.44	н	<1.1	
Basophil Phenotype	e 0.1 ng/ml	0.5		<1	1.44	н	<1.1	
Antigen 1:Peanuts								
Basophil Phenotype	10,000 ng/ml	40.7	H	<1	2.93 H	H	<1.1	
Basophil Phenotype	100 ng/ml	30.2	Н	/ <1	2.10 F	H	<1.1	
Antigen 2: Sesame	•							
Basophil Phenotype	10,000 ng/ml	60.7	Н	<1	2.69 H	1	<1.1	
Basophil Phenotype	100 ng/ml	1.5 H	H	<1	0.84		<1.1	

CD8+ T-Cells & OIT



Low CD8+ T-Cells = OIT SU

- SU is favored by Lower frequencies of naïve CD8+ T cells and terminally differentiated CD57+CD8+ T cell subsets at baseline (pre-OIT) are associated with SU
- Higher frequencies of IL-4+ and IFNγ+ CD4+ T cells post-OIT are negatively correlated with SU

CD8+ T cell differentiation status correlates with the feasibility of sustained unresponsiveness following oral immunotherapy. Abhinav Kaushik... Nature Communications. https://doi.org/10.1038/s41467-022-34222-8

EoP - Eosinophil Progenitors

- 1. Flow Cytometry Whole Blood
- 2. CD34+ cells
- **3. EoPs elevated with EoE**
- 4. Not increased with ELORS (observation)
- 5. EoP numbers match with endoscopic biopsy numbers
- 6. EoPs decrease with improved EoE symptoms and reduction in biopsy Eos

EoP - Eosinophil Progenitors

1

Eosinophil progenitor levels are increased in patients with active pediatric eosinophilic esophagitis





Monitoring Eosinophilic Esophagitis Disease Activity With Blood Eosinophil Progenitor Levels

*Anna Henderson, [†]Adam Magier, [†]Justin T. Schwartz, ^{‡||}Lisa J. Martin, ^{§||}Margaret H. Collins,



Eosinophil progenitor levels correlate with tissue pathology in pediatric eosinophilic esophagitis



NYAIRL - EoP Results

Immunophenotyping Test Results

Gender: male



Clinical Summary

immune evaluation	Research
Test Interpretations	
EoP: 254 cells/mL	N < 15 cells/ml
EoP: 254 cells/mL	N < 15 cells/ml

Recommendations:

increase in peripheral blood eosinophil progenitor cells

Covered Discussion

- Pre-procedure testing
- Monitoring tests
- Frequency of testing
- Response to test results
- Costs of testing
- Outcome Prediction with each tests
- Clinical Observations
- Experience

- Skin Tests
- CBC with Diff
- slgE, Total lgE
- Components IgE
- IgG4
- Vitamin D Level
- BAT, MAT
- Epitope testing
- CD8+T-cells
- EoP

Credits - Thank You



- Dr. Wasserman
- Dr. Jones
- Dr. Siri
- Dr. Sriaroon
- Dr. Alpan
- Dr. Agrawal

- My Teams at ...
- New York Food Allergy
- NYAIRL
- Amerimmune
- Global Food Initiative
- Global Food Foundation