SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

The Big 8: Advances in Food Allergy Risk Assessment and Management

October 11, 2018

Conflict of Interest Statement

SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

Food Allergy Prevention and Treatment: Where We Stand

Matthew Greenhawt, MD, MBA, MSc
Associate Professor of Pediatrics
Director, Food Challenge and Research Unit
Section of Allergy/Immunology
Children's Hospital Colorado
University of Colorado School of Medicine

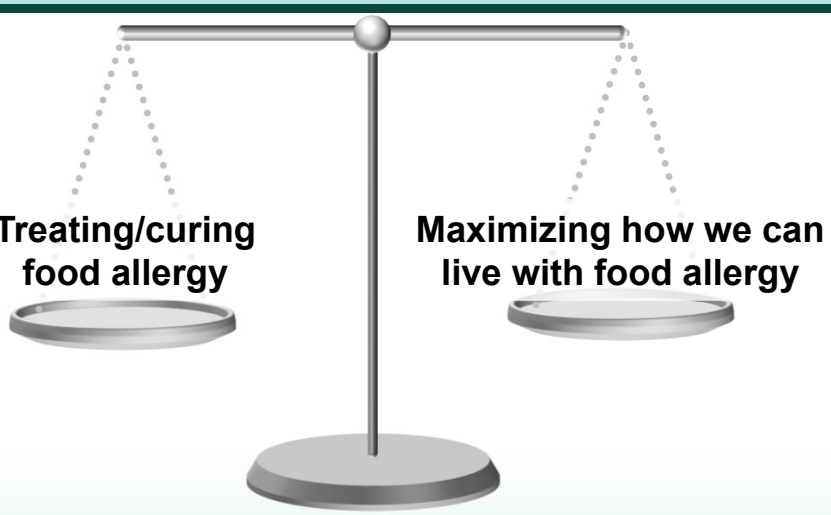
Children's Hospital Colorado

School of Medicine
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Disclosures

- Member, Joint Task Force on Allergy Practice Parameters
- Member of Nutricia, DBV, Aimmune, Kaleo and Monsanto specialty advisory boards and has received honorarium
- Co-chair, Nestle international consensus panel on the use of hydrolyzed formula and received honorarium
- Member, CSACI Food Allergy in Schools Guideline Panel
- Member of the Medical Advisory team for the Allergy and Asthma Foundation of America and the International Association for Food Protein Enterocolitis (nonfinancial)
- Has received honorarium from Thermo Fisher, Symbiotix, Hybrid Health, ClinicalMind, Vindico, Before Brands, multiple state allergy societies for CME/non-CME presentations
- Consultant to Aimmune, Intrommune, Thermo Fisher
- Receiving support from K08-HS024599 (Agency for Healthcare Quality and Research)
- Member of AAAAI EGID, Anaphylaxis, Adverse Reaction to Food committees
- Co-chair, AAAAI Primary Prevention of Food Allergy Working Group; Co-chair, AAAAI Oral Immunotherapy Office-based Practice Working Group
- Member ACAAI Annual Meeting Planning Committee, Chair, GI/Food Allergy Track chair; Chair, Food Allergy Committee
- ACAAI representative to consensus statement on interim consensus on early peanut introduction guidelines
- Member, NIAID Expert Panel on early introduction of peanut to prevent peanut allergy
- Associate Editor, *Annals of Allergy, Asthma, and Immunology*
- Editorial board: *Allergy and Rhinology*; *Medscape Pediatrics*; *Infectious Diseases in Children*
- Member, Scientific Advisory Council, National Peanut Board
- Member, EAACI Task Force on Nutrition and Immunomodulation

A Delicate Balance



Choosing Treatment vs Avoidance

- Caregivers are faced with many decisions
  - May focus on the perceived benefit vs accidental death
  - May prefer to avoid therapy that becomes burdensome
  - May prefer to avoid costly therapy, or not care about cost
  - May have realistic or unrealistic expectations
  - May feel that doing “something” is better than avoidance
- Have to define their expectations and goals
- We can’t judge or prescribe—we are guides
- But, we must inform what would work best
  - If that is even possible!

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Fast-tracked Approaches to Treatment

Oral and Epicutaneous Immunotherapy

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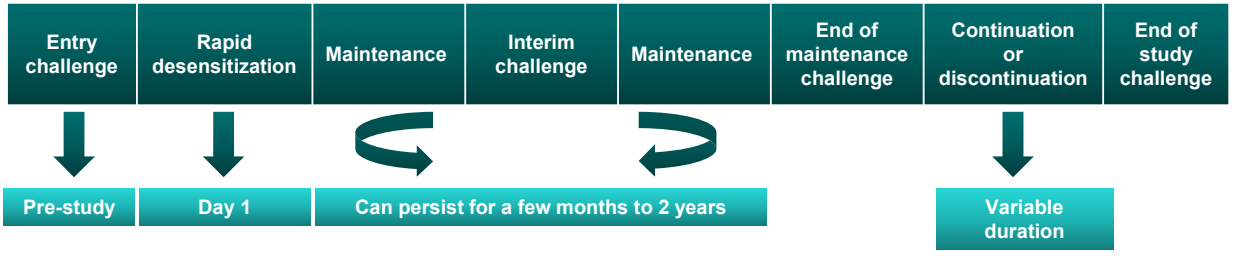
OIT: What Do We Know?

- OIT involves slow medically supervised re-feeding of increasing doses of one's allergen
- Many achieve some degree of desensitization
  - Threshold increased for most, but not all, but few develop sustained unresponsiveness
  - No indication of the duration of therapy, or how long the effects last
- Fairly equal effects were seen with milk, egg, peanut in ability to achieve desensitization
- Markers of allergen sensitivity diminish significantly
  - See shift in allergen-specific IgE >IgG_4 and part of allergen recognized
- See variable effect of immune cell shut down
  - No consistent biomarker pattern shown, but are many targets of interest

Buchanan et al *J Allergy Clin Immunol* 2007; 119: 199-205; Blumchen et al *J Allergy Clin Immunol* 2010: 126: 83-91. Hofman et al. *J Allergy Clin Immunol* 2009: 124: 1154-60. Jones SM et al *J Allergy Clin Immunol* 2009: 124: 292-300. Skripak et al *J Allergy Clin Immunol* 2008; 122: 1154-60; Narisety et al *J Allergy Clin Immunol* 2009; 124: 610-12. Varshney et al *J Allergy Clin Immunol* 2011: 127: 654-60. Kim et al *J Allergy Clin Immunol* 2011; 127 640-6. Burks et al. *N Engl J Med* 2012; 367:233-243. Fleischer et al *J Allergy Clin Immunol* 2013: 131: 119-27

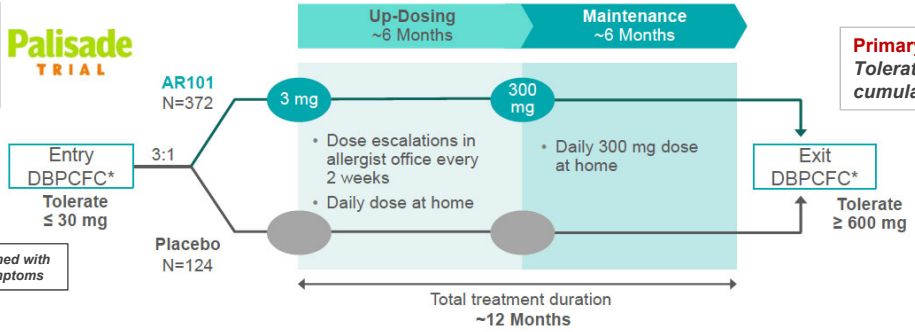
"Typical" OIT Protocol



Buchanan et al *J Allergy Clin Immunol* 2007; 119: 199-205; Blumchen et al *J Allergy Clin Immunol* 2010: 126: 83-91. Hofman et al. *J Allergy Clin Immunol* 2009: 124: 1154-60. Jones SM et al *J Allergy Clin Immunol* 2009: 124: 292-300. Skripak et al *J Allergy Clin Immunol* 2008; 122: 1154-60; Narisety et al *J Allergy Clin Immunol* 2009; 124: 610-12. Varshney et al *J Allergy Clin Immunol* 2011: 127: 654-60. Kim et al *J Allergy Clin Immunol* 2011; 127 640-6. Burks et al. *N Engl J Med* 2012; 367:233-243. Fleischer et al *J Allergy Clin Immunol* 2013: 131: 119-27

PALISADES Entry Characteristics

Key Inclusion Criterion: ***Tolerate ≤43 mg cumulative dose***



Primary Endpoint: ***Tolerate 1043 mg cumulative dose***

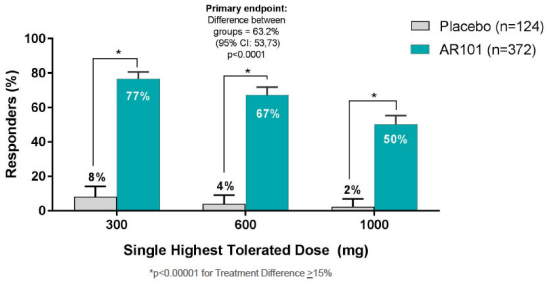
- 90% were ages 4-17 years
- 72% had history of anaphylaxis
- 53% had asthma
- 66% with multiple food allergies
- 43% had peanut sIgE > 100 KU/L
- Median entry OFC challenge tolerance was 10mg (1/30th peanut)

Jones et al. PALISADES Phase III data presentation, 2018 AAAAI. Obtained from www.aimmune.com publically available slide deck

PALISADES Main Results

Intention to treat population

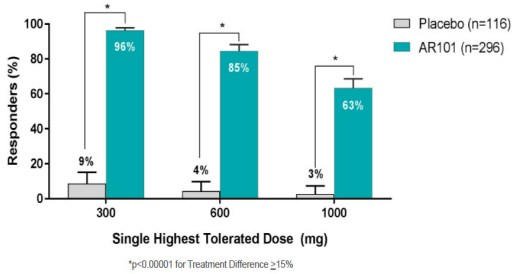
Patients Ages 4-17 Who Tolerated Each Dose Level at Exit DBPCFC



- NNT of 1.58 (ARR 63.2%) for primary endpoint
- NNT of 2.08 (ARR 48%) for secondary endpoint
- 44% with sIgE >100 kU/L tolerated 1000mg

Per Protocol Population ("completers")

Patients Ages 4-17 Who Tolerated Each Dose Level at Exit DBPCFC

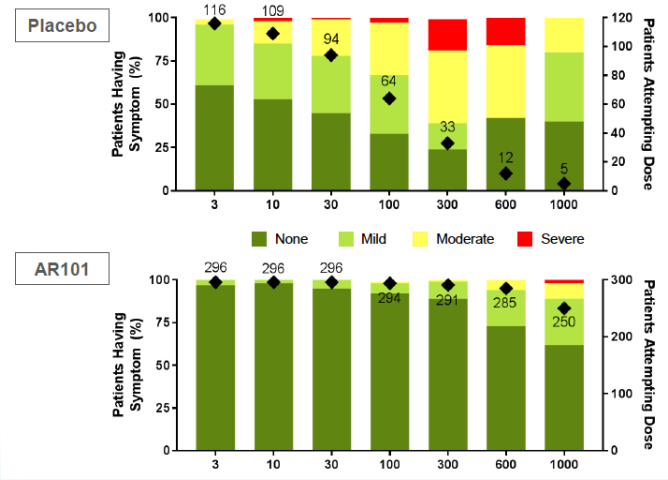


- NNT of 1.23 (ARR 82%) for primary endpoint
- NNT of 1.66 (ARR 60%) for secondary endpoint
- 58% sIgE > 100kU/L overall tolerated 1000mg

NNT in the 18-55y age group was 1.43, but placebo response was 15.4% (~3.5x the younger age group)

Jones et al. PALISADES Phase III data presentation, 2018 AAAAI. Obtained from www.aimmune.com publically available slide deck

PALISADES End OFC Characteristics



Epinephrine Use†	AR101	Placebo
None	268 (91%)	54 (47%)
1	25 (8%)	43 (37%)
2	3 (1%)*	17 (15%)
≥ 3	0	2 (2%)

†p<0.0001 for overall between-group difference
* One patient at 600 mg and two patients at 1000 mg

Key Findings

Compared to placebo, the AR101 group:

1. Developed fewer moderate and severe symptoms;
2. Required more peanut exposure for the onset of symptoms;
3. Was more likely to complete the challenge;
4. Needed less epinephrine

Jones et al. PALISADES Phase III data presentation, 2018 AAAAI. Obtained from www.aimmune.com publically available slide deck

PALISADES Safety

	AR101 (N=372)	
	%	N
Total discontinuations regardless of causality	20.4%	76
Discontinuations not related to adverse events	8.0%	30
Discontinuations related to adverse events	12.4%	46
• Gastrointestinal	6.7%	25
• Systemic hypersensitivity reactions	2.7%	10
• Respiratory system	1.1%	4
• Cutaneous	0.8%	3
• Other (e.g., eye pruritus)	1.1%	4

62 of the 76 dropouts (~82%) occurred during up-dosing

7 were anaphylaxis (6 mild or moderate, 1 severe)

- 9 SAE in 8 participants (2.2%), 1 SAE in placebo, no fatalities
- 4 events considered related
- 5 events led to discontinuation
- 1 case of anaphylaxis in early maintenance (high baseline sIgE)
- 1 case of EoE developed, patient withdrew
- 14.5% experienced investigator reported systemic hypersensitivity reactions, 98% of which were considered mild or moderate

Jones et al. PALISADES Phase III data presentation, 2018 AAAAI. Obtained from www.aimmune.com publically available slide deck

PPOIT and 4-Year Outcomes

- Teng et al. demonstrated efficacy of 18 months of a novel peanut OIT + Lactobacillus Rhamnossus CGMCC combination in a 2015 double blind, randomized controlled study
- Initial effect demonstrated successful desensitization in 26/29 PPOIT patients and 2 week sustained unresponsiveness in 23/28 of these patients
- Probiotic dose the equivalent of “20 tubs” of yogurt/day!
- Now, following 48 of the original 56 participants for 4 years after discontinuation of OIT
- N=24 PPOIT and n=24 placebo patients followed after exit food challenge
- No set protocol for peanut ingestion in the PPOIT group
- At 4 years, both groups asked to discontinue peanut ingestion for 8 weeks and repeat challenge

Hsiao K-C et al *Lancet Child Adolesc Health* 2017; 1: 97-105.

PPOIT and 4-Year Outcomes

- Noted 16/24 PPOIT vs. 1/24 subjects were regularly ingesting peanut ad libitum (NNT 1.6)
- Half of the PPOIT subjects were eating >2g/week(46% 1x/wk, 29% 1-2x/wk, 17% 3x or more/wk, with 16/20 PPOIT subjects consuming peanut "regularly", and 20/24 reporting no reactions since stopping PPOIT therapy
- N=27 agreed to the 8 week additional discontinuation. Of these 7/12 PPOIT vs. 1/15 placebo tolerated the challenge and resumed eating peanut (NNT=1.9)
- 7/12 who underwent PPOIT ate peanut ad lib for 4 years, then agreed to stop eating peanut for another 8 weeks demonstrated sustained unresponsiveness. ***This pattern mimics a non-allergic individual's consumption!***
- Study issues: no initial challenge for the 2015 study, some degree of drop out, small #'s
- ***The implications of this effect, if replicated, may completely change the game***

Hsiao K-C et al *Lancet Child Adolesc Health* 2017; 1: 97-105..

Other Published Peanut OIT Trials

Reference	Year	Design	Sample size	Subject age (y)	Maintenance dose (mg)	Duration	Primary outcome
Jones et al	2009	Open label	29	1-16	1800	36 mo	93% passed 3.9-g peanut OFC
Blumchen et al	2010	Randomized open label	23	3-14	500	7-d Rush escalation, 8-wk maintenance period	64% reached maintenance of 500 mg of peanut
Varshney et al	2011	Randomized, placebo controlled	19	3-11	2000	48 wk	84% passed 5000-mg peanut OFC
Anagnostou et al	2011	Open label	22	4-18	800	32 wk	64% tolerated 6.6-g OFC
Anagnostou et al	2014	Randomized, controlled	39	7-16	800	26 wk	62% tolerated 1400-mg challenge
Vickery et al	2014	Open label	24	1-16	Up to 4000	Up to 5 y	50% SU to 5000-mg OFC after 4-wk avoidance
Narisety et al	2014	Randomized, placebo controlled	16	7-13	2000	12 mo	OIT > SLIT in OFC threshold, low rate of SU
Factor et al	2012	Open, uncontrolled	93	5-18	450 (3 M&M)	24 wk	90/100 pts able to tolerate 450 mg, showed improvement in pt FAQLQ score. Clinic-based study
Wasserman et al	2014	Open label	352	Median 5-9 y	415-8000	Variable, Weeks-yrs	Real-life experience of 5 practices. 281/352 (80%) reached maintenance. 10% of pts required epi (36/352)
Tang et al	2015	Randomized, placebo controlled	62	1-10	2 g with $2x10^2$ CFU *L. rhamnosu*	18 mo	23/28 (82.1%) vs 1/28 (3.6%) achieved SU at 2-5 wk post-discontinuation. 26/29 achieved desensitization.
Vickery et al	2016	Randomized, placebo controlled	40	9-36 mo	300 vs 3000	Up to 3 y	17/20 in 300-mg and 12/17 in 3000-mg arm achieved SU at 4 weeks (29/37 total)

Wood R. *J Allergy Clin Immunology* 2016: 137: 973-82. Tang et al *J Allergy Clin Immuno* 2015; 135: 737-44. Factor J et al. *Ann Allergy Asthma Immunol* 2012; 109: 348-52. Wasserman et al *J Allergy Clin Immunol Pract* 2014; 2; 91-6. Vickery et al *J Allergy Clin Immunol* 2017; 139: 173-181. Hsiao K-C et al *Lancet Child Adolesc Health* 2017; 1: 97-105.

Published Egg and Milk OIT Studies

TABLE II. Egg OIT studies

Reference	Year	Design	Sample size	Subject age (y)	Maintenance dose (g)	Duration (mo)	Primary outcome
Buchanan et al[34]	2007	Open label	7	1-16	0.3	24	57% Passed 8-g OFC
Vickery et al[35]	2010	Open label	8	3-13	0.3-3.6	18-50	75% Passed OFC 1 mo after stopping OIT
Burks et al[26]	2012	Randomized, placebo controlled	40	5-11	1.6	22	75% Passed 10-g OFC but SU in only 28% at 6-8 wk later

TABLE III. Milk OIT studies

Reference	Year	Design	Samples size	Subject age (y)	Maintenance dose	Duration	Primary outcome
Meglio et al[36]	2004	Open label	21	6-10	200 mL	6 mo	72% Desensitization to 200 mL of cow's milk daily
Longo et al[37]	2008	Randomized, open label	30	5-17	150 mL	10-d Rush escalation, 1 y of maintenance	36% Tolerant (≥150 mL) and 54% partially tolerant (5-150 mL)
Skripak et al[38]	2008	Randomized, placebo controlled	13	6-17	500 mg	23 wk	Median OFC threshold increased from 40 to 5,140 mg after OIT
Narisety et al[31]	2009	Open label (follow-up)	13	6-16	500-4,000 mg	3-17 mo	Median OFC threshold of 7,000 mg (with 33% tolerating 16,000 mg)
Pajno et al[40]	2010	Randomized, placebo controlled	15	4-10	200 mL	18 wk	67% Tolerant to 200 mL of cow's milk
Martorell et al[39]	2011	Randomized, placebo controlled	30	2-3	200 mL	1 y	90% Showing complete desensitization
Keet et al[25]	2012	Randomized, placebo controlled	20 for OIT	6-17	1,000-2,000 mg	60 wk	70% Desensitized to 8-g OFC, SU in 40% after 6 wk
Wood et al[41]	2015	Omalizumab DBPC, open-label OIT	57	7-32	3,300 mg	24 mo	80% Desensitized to 10-g OFC, SU in 42% after 8 wk

Wood R. J Allergy Clin Immunology 2016: 137: 973-82

Predicting Symptoms from OIT

Incidence rate ratios of the influence of baseline characteristics on the prevalence of AEs, overall and during the buildup and maintenance phases of OIT

Variable	Overall AEs		Buildup AEs		Maintenance AEs	
	IRR (95% CI)	*P* value	IRR (95% CI)	*P* value	IRR (95% CI)	*P* value
Sex (female compared with male)	0.7 (0.4-1.2)	.24	0.6 (0.3-1.0)	.06	1.2 (0.6-2.4)	.54
Age (per 1-y increase)	1.0 (0.9-1.1)	.89	1.1 (0.9-1.2)	.40	1.1 (1.0-1.2)	.20*
Asthma	0.9 (0.5-1.4)	.55	0.6 (0.4-1.1)	.11	2.3 (1.1-4.9)	.03*
Atopic dermatitis	1.2 (0.6-2.2)	.59	1.2 (0.6-2.3)	.63	1.1 (0.5-2.4)	.89
AR	2.9 (1.6-5.0)	<.001*	2.1 (1.2-3.8)	.01*	6.9 (2.5-18.7)	<.001*
Peanut SPT wheal size (per 5-mm increase)	1.4 (1.1-1.7)	.005*	1.4 (1.1-1.8)	.01*	1.3 (1.0-1.8)	.07*
Log peanut IgE (per log increase)	0.9 (0.7-1.0)	.14	0.9 (0.7-1.0)	.10	0.9 (0.7-1.2)	.44

Virkund et al *J Allergy Clin Immunol* 2017; 139: 882-888.e5.

Predicting Symptoms from OIT

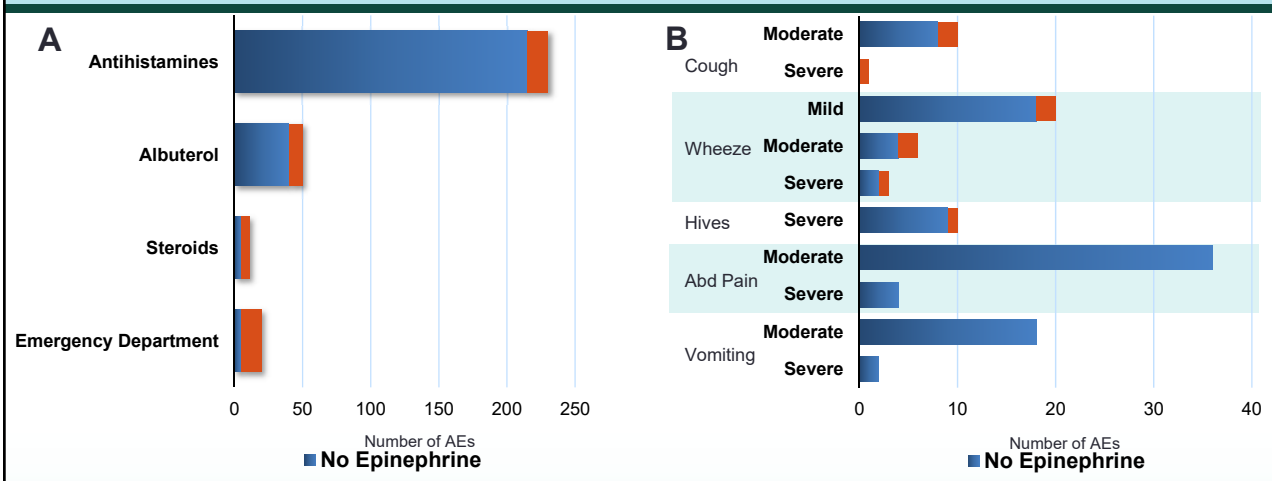


FIG 4. Frequencies of AEs resulting in epinephrine use. Patterns of use of epinephrine concurrently with administration of antihistamines, albuterol, oral corticosteroids, or an ED visit (A), and in response to specific symptoms (cough, wheeze, hives, abdominal [Abd] pain, or vomiting) (B). Overlap of AEs with 2 or more given symptoms (ex: cough and wheeze) may be present.

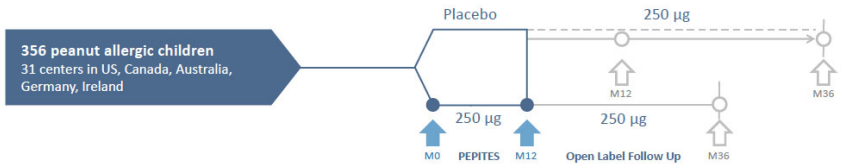
Virkund et al *J Allergy Clin Immunol* 2017; 139: 882-888.e5

EPIT—Where Do We Stand?

- DBV Viaskin MILES and PEPITES in Phase 2/3
- Far fewer published data vs OIT
  - Early data note that 70% had a 10-fold dose increase, no serious AEs
  - MILES data noted all AEs associated with site urticaria/redness
  - Milk EPIT induced T_{regs} protect from anaphylaxis in adoptive transfer
  - Higher numbers of T_{regs} were produced in EPIT vs OIT, persisted after EPIT stopped
  - EPIT was not associated with EoE in murine models vs OIT
- Phase III peanut trial showed significant effect for 250mcg patch with good safety
- Phase II milk trial showed significant effect for 250mcg patch also with good safety

Sampson et al 2016 AAAAI oral abstract; Rutalt et al 2016 AAAAI oral abstract; Mondoulet et al 2016 AAAAI oral abstract; Dioszeghy et al 2016 AAAAI oral abstract; Mondoulet et al 2016 EAACI oral abstract

PEPITES Design



Study Population

Highly allergic patients ages 4-11
- > 0.7 kU/ L peanut-specific IgE and ≥ 6mm or 8 mm SPT* wheal
- Reactive dose at M0 ≤ 300 mg peanut protein (i.e. approx 1 peanut)

Efficacy Endpoints

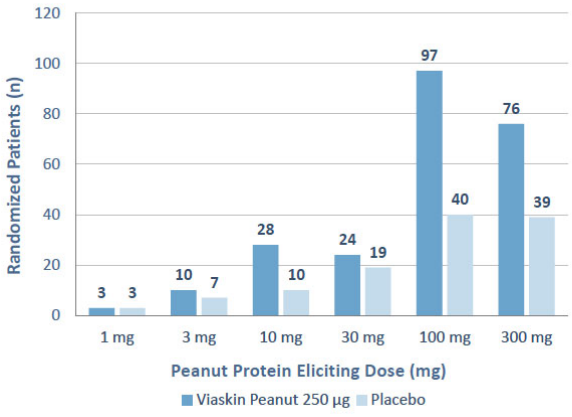
Treatment responder definition:
- Assessed using DBPCFC**
- For subjects with a M0 ED*** ≤ 10mg: responder if ED ≥ 300 mg at M12
- For subjects with a M0 ED > 10mg: responder if ED ≥ 1,000 mg at M12

Key secondary endpoints:
- CRD****, changes in peanut sIgE and sIgG4

OFC protocol

https://www.dbv-technologies.com/wp-content/uploads/2018/04/dbv-technologies-investor-presentation_april-2018.pdf

PEPITES Entry Characteristics



356 Patients Randomized
- Active: 238
- Placebo: 118

Peanut Eliciting Dose (mg)
- Median: 100
- Mean: ~140

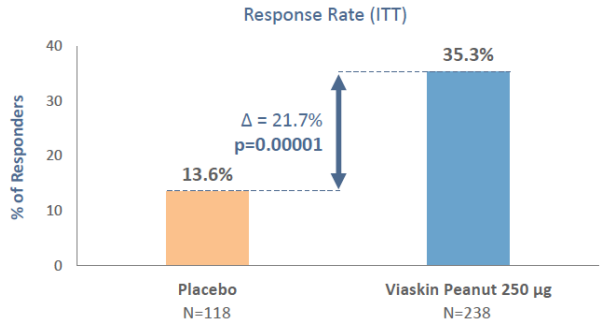
Medical History of Patients

	n	%
Asthma	169	47.5
Eczema/Atopic Dermatitis	218	61.2
Allergic Rhinitis	199	55.9
Polyallergic	305	85.7

https://www.dbv-technologies.com/wp-content/uploads/2018/04/dbv-technologies-investor-presentation_april-2018.pdf

PEPITES Main Results

Response rate was statistically significant, but 15% lower bound of the 95% CI proposed in the SAP submitted to FDA was not reached



NNT 4.6 (ARR 21.7%)

LCL	12.4
UCL	29.8

Differentiated Safety Profile

- Favorable tolerability and compliance observed
- 1.1% dropout due to treatment emergent adverse events (TEAEs)
- Most commonly reported adverse events were application site reactions, which were generally mild to moderate
- Mean patient compliance above 95%

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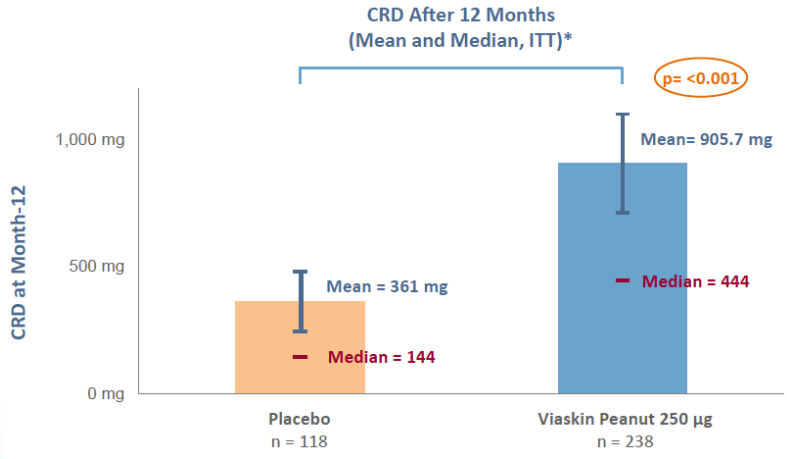
PEPITES Change in Reactive Dose



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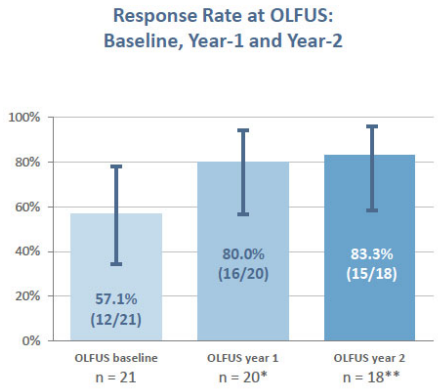
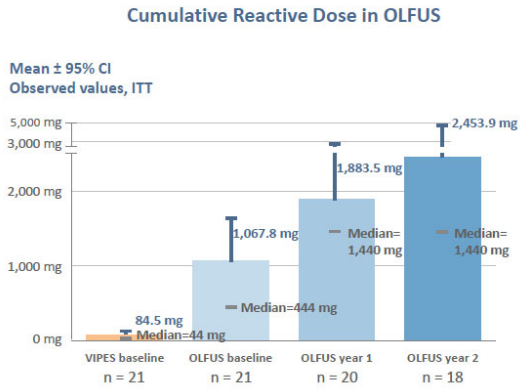
Longer Term Outcomes: VIPES Study

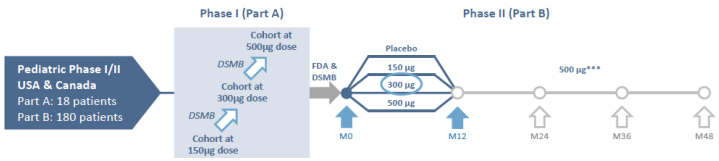




- Unlike in OIT, changes in EPIT may occur over a longer horizon
- Data on mean CRD and response improved through year 2 and 3 of study

https://www.dbv-technologies.com/wp-content/uploads/2018/04/dbv-technologies-investor-presentation_april-2018.pdf

MILES Entry Criteria and Design



Study Population

- Children (2-11) and adolescents (12-17)
- Highly sensitive to milk (≥ 10 kU/L milk-specific IgE and ≥ 6 mm SPT* wheal)
- Reactive dose at baseline (M0) ≤300 mg cow's milk protein (CMP) (~≤9.4 mL of cow's milk)

Efficacy Endpoints

Treatment responder definition at M12:
- ≥ 10-fold increase in CRD** and at least 144 mg of CMP
- OR CRD ≥ 1,444 mg

Key secondary endpoints:
- Change from baseline in IgE, IgG4

198 patients randomized
- 152 Children (2-11)
- 46 Adolescents (12-17)

CRD of Cow's Milk

Mean
- Children: 216.3 mg
- Adolescents: 222.0 mg

Median
- Children: 144 mg
- Adolescents: 144 mg

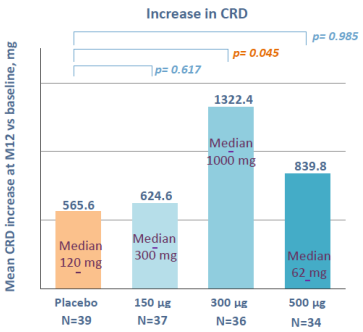
Medical history of patients

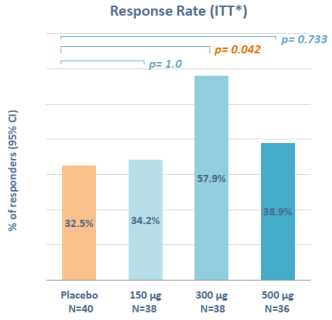
	n	%
Asthma	139	70.2
Atopic Dermatitis	139	70.2
Allergic Rhinitis	144	72.7
Polyallergic	178	89.9

Mean Cow's Milk sIgE
- Children: 135.2 kU/L
- Adolescents: 127.9 kU/L

https://www.dbv-technologies.com/wp-content/uploads/2018/04/dbv-technologies-investor-presentation_april-2018.pdf

MILES Phase II Results





Favorable safety, tolerability and compliance

- Overall discontinuation rate of 4.5%
  - 1.5% dropout due to adverse events
- Most adverse events were related to application site, and were mild to moderate
- No SAEs or epinephrine use related to treatment
- Treatment adherence was high, with a mean patient compliance > 95%

- For the 300ug dose, NNT was 3.93 (ARR 25.4%)
- Unclear why response at 300ug was optimal
- High placebo rate likely reflects difficulty of treating an allergen that has a favorable natural history

https://www.dbv-technologies.com/wp-content/uploads/2018/04/dbv-technologies-investor-presentation_april-2018.pdf

What Motivates Parents to Seek Therapy

Study Features

- 45 minute semi-structured interviews transcribed verbatim
- 22 patients interviewed (6 OIT, 16 EPIT)
- Questions probed caregiver motivations/goals for therapy, treatment expectations and trade-offs, family lifestyle, and emotions surrounding life with peanut allergy.

Summary of Key Themes	
Theme 1	Peanut allergy therapy only needs to provided minimal protection with minimal risks a. Desire for a buffer b. Understanding that therapy wasn't a cure.
Theme 2	How the buffer translates to meaningful impact on quality of life a. Decreasing reaction severity b. Enhancing social activity
Theme 3	Helping others by advancing science

Caregiver definitions of what a "buffer" represents, with example quotes	
Example Definition	Sample Quotation
The child would tolerate ingestion of a higher amount of total peanut protein than their pre-therapy baseline (which was measured as a primary outcome for both the OIT and EPIT trials)	"We'd like him to be bite proof."
The child would have less severe symptoms resulting from ingestion than at pre-therapy baseline;	"So my goal and his goal is that if there's ever accidental exposure…that it's not gonna end up landing him in the emergency room…It's just if we could just curb the reactions a little bit and minimize the likelihood of them that's kind of our goal." "We'd like him to be able to accidentally ingest his allergen and not have anaphylaxis. And that would be, if we could get there I would consider that a success."
Any resulting allergic reaction to peanut would take longer to manifest and peak (a "slower reaction"), allowing for more time for someone to assess the child and administer treatment	"We've got a chance if he gets exposed that it doesn't mean he's going to die. It means we see the symptoms, we catch them quick enough, and hopefully everything will be okay."

Greenhawt et al. Submitted.
Greenhawt et al J Allergy Clin Immunol 2018; 141(2): Supplement, AB256; https://doi.org/10.1016/j.jaci.2017.12.814

Drivers of Food Allergy Quality of Life

The Facts

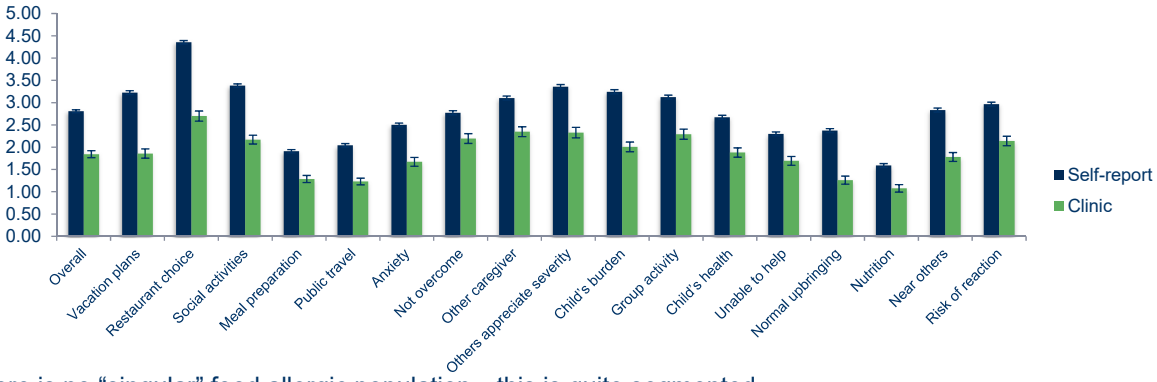
- 8% prevalence among children
  - No known cure or treatment
  - Some allergies are lifelong
- Reaction severity is poorly predictable
- Accidental reactions from trace amounts may occur
- Associated with anxiety and stress
- High cost to society
  - $24.8B/year ($4,184/patient/year)

The Burdens

- Fear of accidental reaction, and persistent vigilance toward prevention
- Fear of hidden ingredients
- Fear of being able to treat a reaction
- Burden of no cure for the disease
- Burden of food avoidance/label reading
- Limitation of activity/travel
- Social stigma/inclusion and interactions
- Bullying
- Empowerment (or lack thereof)

Gupta et al JAMA Pediatr 2013; 167: 1026-31.
Greenhawt M. *Ann Allergy Asthma Immunol* 2014; 113: 506-12.
Sampson HA *J Allergy Clin Immunol* 2014; 134: 1016-25.
Anagnostou et al *Lancet* 2014: http://dx.doi.org/10.1016/S0140-6736(13)62301-6.

QoL is Different Between Populations



- There is no "singular" food allergic population—this is quite segmented
- Each segment of this population feels this burden differentially
- Total and domain specific QoL worse in self-reported population
- Noted also for anaphylaxis, epinephrine use, and by allergen (milk/egg worse than peanut/tree nut)
- **Why would we expect attitudes and preferences for treatment to be any less segmented?**

Ward CA and Greenhawt MJ. J Allergy Clin Immunol Pract 2016; 4: 257-64.e3

QoL as an OIT Outcome Measure

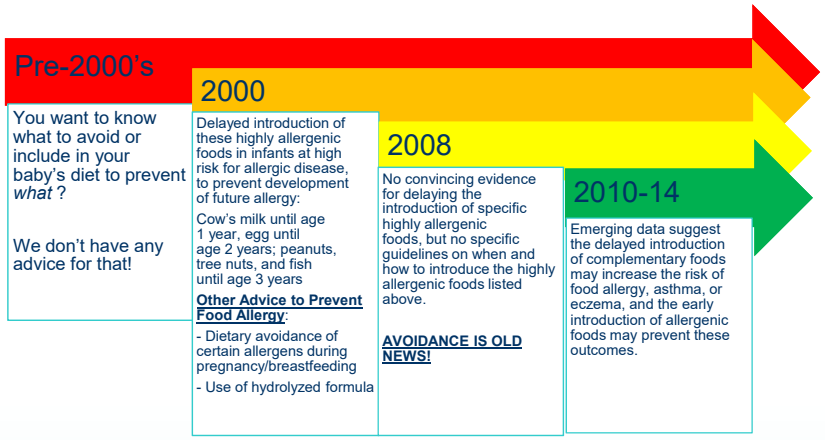
- Limited patient reported outcomes from OIT
  - Stanford group: Significant improvement vs. baseline over time (24m), all domains/times, more change in older pts or those undergoing >4 food OIT (both multi-food and omalizumab trials)
  - Factor et al: QoL noted to significantly improve after reaching 450mg maintenance dose
  - Anagnstou et al (STOP II trial): QoL scores noted to improve after OIT to 800mg peanut maintenance dose
  - Epstein Rigbi et al: selected QoL domains improve during buildup to maintenance in some, though some with good baseline QOL deteriorated and some with poor baseline QOL improved
- Being assessed in current OIT and EPIT trials, but using a parent proxy index, or only assessing older child's impression. Not assessing caregiver impact

Arasi et al Allergy Asthma Clin Immunol 2014; 10: 57-64
Otani et al Allergy Asthma Clin Immunol 2014; 10; 25-32
Anagnostou et al Lancet 2014; 383: 1297-1304
Factor et al Ann Allergy Asthma Immunol 2012; 109: 348-52

QoL and Treatment: Needs Assessment

- Understand what contributes to poor QoL so we know what we are modifying
  - Weight/importance of child vs. caregiver QoL with respect to treatment
  - Bark worse than the bite--disease perception vs. reality must be better aligned
- Understand heterogeneity in QoL
  - Determine effect of MD knowledge, practice variation
- Integration of QoL as a clinical outcome
  - Is it QoL that changes, or their self-efficacy, or something else
  - Parent proxy child QoL is not the same as the child's QoL, or the parent QoL.
  - **Must move towards developing more specific interventions and tools to improve QoL**

The Evolving Saga of Prevention Advice



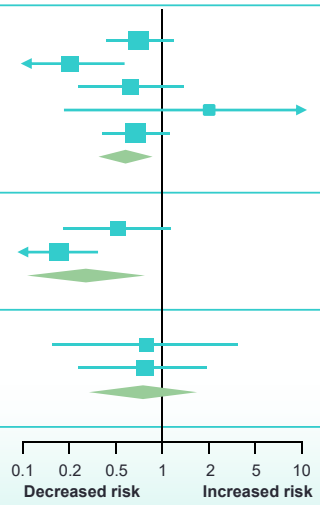
- But, since 2008, 7 major studies have been performed that provide us much better data….

AAP Committee on Nutrition. *Pediatrics*. 2000;106(2 pt 1):346-349.
Greer FR, et al. *Pediatrics*. 2008;121(1):183-191.
Fleischer DM et al.. J Allergy Clin Immunol Pract 2013; 1: 29-36.

Study	Full Title	Study Type	Population	Intervention	Primary Outcome	Results
LEAP (UK)	Learning Early About Peanut Allergy	Non-blinded RCT (n=640)	**High-risk** infants • moderate to severe eczema and/or egg allergy	• **Thrice weekly consumption of 2g of peanut** protein vs complete avoidance of peanut after randomization at 4-11 months, through 60 months of life	**IgE-mediated peanut allergy** based on OFC at month 60	• ITT analysis showed prevalence of peanut allergy 13.7% in the avoidance group vs 1.9% in the consumption group (p<0.001)
EAT (UK)	Enquiring About Tolerance	Non-blinded RCT (n=1303)	**Standard risk:** • exclusively breastfed until allergenic foods introduced	• **Early introduction group (EIG) introduced 2g of protein twice weekly at 3 months of peanut, cooked egg, cow's milk, sesame, whitefish, wheat** • **Standard introduction group (SIG)** at 6 months of above 6 foods	**IgE-mediated food allergy to at least 1 of the 6 allergens** at 1 or 3 years of age based n OFC	• ITT analysis showed no difference in food allergy between EIG vs SIG • PP analysis showed significantly less prevalence of peanut allergy (p=0.003) and egg allergy (p=0.009) in EIG vs SIG
STAR (Australia)	Solids Timing for Allergy Reduction	Blinded RPCT (n=86)	**High-risk** infants with moderate to severe eczema	• **Daily consumption of egg** vs placebo powder from 4-8 months • 0.9 g raw whole egg powder daily **(0.4 g protein/day)** • Cooked egg at 8 months	**IgE-mediated egg allergy** at 12 months based on positive SPT and egg OFC	• Study terminated early: 1/3 of patients reacted to egg at entry OFC • At 12 months, 33% had egg allergy in egg group vs 51% in control (not significant)
STEP (Australia)	Starting Time for Egg Protein	Blinded RPCT (n=820)	**Intermediate risk**: • atopic moms (allergic disease + positive envir SPT • Infants: no allergic dz	• **Daily consumption of egg** vs placebo powder from 4-6.5 months • 0.9 g raw whole egg powder daily **(0.4 g protein/day)**	**IgE-mediated egg allergy** at 12 months based on positive SPT and egg OFC	• No significant differences in egg allergy between groups • No anaphylactic reactions at initial egg intro
BEAT (Australia)	Beating Egg Allergy Trial	Blinded RPCT (n=319)	**Intermediate risk**: • Infants with 1st degree relative with atopy • Infants: neg egg SPT	• **Daily consumption of egg** vs placebo powder at 4 months • **350 mg protein daily** raw whole egg powder • Cooked egg at 8 months	**Sensitization to egg** by SPT at 12 months of age	• Subjects in egg group vs placebo had significantly less egg sensitization (10.7% vs 20.5%, p=0.03) • No harm with egg intro
HEAP (Germany)	Hens Egg Allergy Prevention	Blinded RPCT (n=406)	• **Normal risk** general population • Infants with IgE <0.35 kU/L at enrollment	• **Thrice weekly 2.5 g egg protein** from 4-6 months of age until 12 months	**Sensitization to egg** based on egg IgE ≥0.35 kU/L at 12 months of age	• No evidence of preventing egg sensitization or allergy • High rate of anaphylaxis at egg introduction at entry
PETIT (Japan)	Preventing egg allergy in infants with AD	Blinded RCT (n=121)	**High-risk** infants with atopic dermatitis	• Daily consumption of **50 mg** heated egg from 6-9 months • Daily consumption of **250 mg** heated egg from 9-12 months	**IgE-mediated egg allergy** at 12 months of age based on OFC	• Prevalence of egg allergy 37.7% in placebo vs 8.3% in egg group (p=0.0013) • No SAEs

Pooled Data of Early Introduction Trials

Study	Early Events, n	Early Total, n	Late Events, n	Late Total, n	RR	95% CI	Weight (random)
Outcome = Egg Allergy							
Perkin 2016	21	569	32	596	0.69	[0.40, 1.18]	30.9%
Natsume 2016	5	60	23	61	0.22	[0.09, 0.54]	16.7%
Tan 2016	8	130	13	124	0.59	[0.25, 1.37]	18.2%
Bellach 2015	2	142	1	156	2.20	[0.20, 23.97]	3.1%
Palmer 2013	14	42	18	35	0.65	[0.38, 1.11]	31.1%
Random effects model		**943**		**972**	**0.56**	**[0.36, 0.87]**	**100%**
Heterogeneity: I^2=35.8%, P=0.1829							
Outcome = Peanut Allergy							
Perkin 2016	7	571	15	597	0.49	[0.20, 1.19]	45%
Du Toit 2015	10	312	54	313	0.19	[0.10, 0.36]	55%
Random effects model		**883**		**910**	**0.29**	**[0.11, 0.74]**	**100%**
Heterogeneity: I^2=66.1%, P=0.0857							
Outcome = Milk Allergy							
Perkin 2016	3	569	4	597	0.79	[0.18, 3.50]	32.7%
Lowe 2011	6	193	8	191	0.74	[0.26, 2.10]	67.3%
Random effects model		**762**		**788**	**0.76**	**[0.32, 1.78]**	**100.0%**
Heterogeneity: I^2=0%, P=0.9498							



Ierodiakonou D et al *JAMA* 2016; 316: 1181-92

So What Do These Data Suggest?

- UK Food Standards sponsored a recent evidence review

  --16,289 titles screened, 51 studies identified

- "Moderate certainty evidence" from 5 egg trials for protective benefit of early egg introduction at 4-6 months

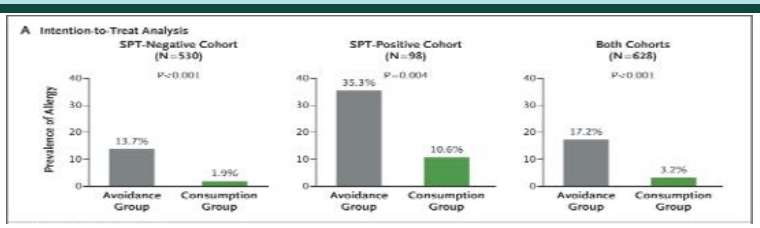
  --44% lower risk, prevents 24 cases of allergy per 1000 children

- "Moderate certainty evidence" from 2 trials for protective benefit for early peanut introduction

  --71% lower risk, prevents 18 cases of allergy per 1000 children

Ierodiakonou D et al *JAMA* 2016; 316: 1181-92

LEAP Results Influence on NIAID Policy



11.8% difference 24.7% difference 14% difference

The study effect, in plain English…….	Negative skin test	Positive skin test	Total
Feed this many infants peanuts to prevent one case of peanut allergy	8.5	4	7.1

Take home messages

- This worked very well—there was clear benefit for early introduction vs. avoidance, good NNT is <10
- This worked even if you had a positive skin test, showing it halted an allergy-in-progress
- The effect was not temporary—even after not eating peanut for a year, in each group there were only 3 new cases of peanut allergy (LEAP-On study)

Du Toit G et al. N Engl J Med 2015;372:803-813
DuToit et al N Engl J Med 2016; 10.1056/NEJMoa1514209

NIAID Peanut Prevention Addendum

Addendum Guideline	Infant Criteria	Recommendations	Earliest Recommended Age of Peanut Introduction
1	Severe eczema, egg allergy or both	Strongly consider evaluation by sIgE and/or SPT, and if necessary an oral food challenge. Based on test results, introduce peanut containing foods	4 to 6 months
2	Mild to moderate eczema	Introduce peanut-containing foods	Around 6 months
3	No eczema or any food allergy	Introduce peanut-containing foods	Timing of introduction is age appropriate and in accordance with family preferences and cultural practices

Toigas et al. J Allergy Clin Immunol 2017; 139: 29–44

Comparing NIAID vs. Other Guidelines

Australia/New Zealand (ASCIA)

- When your infant is ready, at around 6 months, but not before 4 months, start to introduce a variety of solid foods, starting with iron-rich foods, while continuing breast-feeding.
- All infants should be given allergenic solid foods including peanut butter, cooked egg, dairy, and wheat products in the first year of life. This includes infants at high risk of allergy.
- Hydrolyzed (partially or extensively) infant formula is not recommended for the prevention of allergic disease.
- No specific screening, testing, evaluation recommendations prior to introduction

UK Department of Health

- Exclusive breastfeeding for around the first six months of life.
- Foods containing peanut and hen's egg need not be differentiated from other complementary foods and should be introduced in an age-appropriate form from around six months of age, alongside continued breastfeeding, at a time and in a manner to suit both the family and individual child.
- The deliberate exclusion of peanut or hen's egg beyond six to twelve months of age may increase the risk of allergy
- Once introduced, and where tolerated, these foods should be part of the infant's usual diet, to suit both the individual child and family.
- Families of infants with a history of early-onset eczema or suspected food allergy may wish to seek medical advice before introducing these foods.

Netting et al J Allergy Clin Immunol Pract. 2017. In Press http://dx.doi.org/10.1016/j.jaip.2017.03.013
https://col.food.gov.uk/sites/default/files/jointsacncotallergystatementfinal2.pdf

Primary Prevention with Other Foods

- EAT study: Weak but significant effects for egg and peanut only in per protocol. No effect for any other allergen, ? shows non-inferiority
  - 68% unable to follow protocol in the early intro group. Influenced by perceived sx, nonwhite race, poor caregiver QoL, eczema. Adherence: milk 85%, peanut 62%, fish 60%, sesame 51%, egg 43%
- Milk:
  - Katz et al Israeli observational birth-cohort of 13,019 infants. 1 yr cumulative incidence of milk allergy 0.5% (66/13,019), but 0.05% (introduction < 14d) vs. 1.75% (105-194d) (OR 19.3)
  - Onizawa et al. Japanese retrospective case-control study of 51 milk allergic vs 102 controls and 32 egg allergic children. 69% of the CMA children had milk in the first month of life versus 88% in the non-CMA infants (OR 4507)
- Fish:
  - Finnish cohort has suggested fish consumption in 1st year associated with reduced risk of rhinitis, eczema, asthma, and food/pollen sensitization at 4y (RR=0.76)

Katz et al J Allergy Clin Immunology 2010; 126: 77-82
Kull I et al. Allergy 2008; 61: 1009-1015
Perkin et al NEJM 2016; Dl: 10.1056/NEJMoa1514210
Onizawa et al J Allergy Clin Immunol Pract 2016;4:481-8

The Role of Dietary Diversity

- Timing of solid food introduction may not be the only factor promoting tolerance
  - Diverse exposure to a variety of foods in early childhood may be equally as important
- Roduit et al: diversity of commonly eaten food in Swiss infants in 1st year of life showed protective association against asthma, eczema and food allergy at age 6
- Nwaru et al: diversity of commonly eaten food in Finnish infants at 3 mo showed protective association against risk of "atopic sensitization" including foods at age 5
- Maslin et al: in infants with eczema, a more diverse diet in first year of life prevented challenge proven food allergy at age 3
- Perkin et al: both cohorts exposed to 5 foods between 3-6 mo or 6-9mo, very low rates of food allergy developed overall
- No interventional trial done to show potential causal effects, however

Nwaru B et al. J Allergy Clin Immunol 2014; 133: 1084-91
Roduit C, et al. J Allergy Clin Immunol 2014; 133:1056-64.
Maslin et al. FAIR cohort data. INFLAME meeting, May 5, 2017.
Perkin et al. New Eng J Med 2016; 374: 1733-43

Conclusions

- Multiple potential approaches to treating food allergy may exist
- None have long-term efficacy
- Quality of life as a treatment outcome is still being defined
- Entering into a therapy is a very complex decision
- Key is to understand the caregiver goals for seeking therapy
- Prevention strategies for early allergen introduction expected to help decrease the ultimate number of food allergic individuals
- Early introduction may not be the only important dietary factor associated with prevention