

GROUNDBREAKING ASTHMA AND ALLERGY ARTICLES FROM 2015

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Disclosures

- I have no relevant financial relationships with the manufacturers(s) of any commercial products(s) and/or provider of commercial services discussed in this CME activity.
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Objectives

- Understand the role of early introduction of peanut in prevention of peanut allergy
- Recommend therapy for toddlers with recurrent wheezing through an individualized approach
- Utilize food allergen IgE tests appropriately and interpret within clinical history

Poll # 1

- At what age do you recommend parents introduce age appropriate peanut containing foods to their children?
 - 4-6 months
 - 6-9 months
 - 9-12 months
 - 2 years old
 - 3 years old

The LEAP Study

The **NEW ENGLAND**
JOURNAL *of* **MEDICINE**

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Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

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Food Introduction - Background

2000 Recommendations from American Academy of Pediatrics

- Delay introduction of solid foods until 4-6 mos
- Use hypo-allergenic formula for at risk infants
- Introduce whole cow's milk at 12 mos
- Avoid eggs until 2 years of age
- Avoid peanuts, tree nuts, fish until 3 years of age
- Mothers of at-risk infants should avoid consumption of peanuts during pregnancy and while breast feeding

(Based on few studies with various limitations)

2008 vs 2000 AAP Recommendations

Intervention	2008	2000
Define 'high risk'	Parent or sibling with atopy	Both parents or 1 parent and sibling
Avoidance of foods during pregnancy	Lack of evidence	Possibly peanut
Exclusive breast feeding until	Evidence for 3-4 mos	6 months
Avoidance of foods during lactation	Some evidence for reduced atopic dermatitis	Peanuts, tree nuts and consider egg, milk, fish and "other foods"
Prevention formulas	Certain hydrolysates may delay onset compared with cow's milk based, not soy	"Hypoallergenic" formulas, not soy
Types of solid foods	Evidence to wait until 4-6 mos; no evidence for specific foods	No solids until 6 mos, milk til 1 yr, egg til 2 yrs, peanuts, nuts, fish til 3 yrs

What's the Deal with Peanuts?

- Prevalence of food allergy has doubled in past decade
- Food allergy:
 - Overall, affects 5-8% of children
 - Peanut allergy ~1%
- 2008 Study: Prevalence of peanut allergy in Israeli children 10-fold less than in United Kingdom
 - Adjusted Risk Ratio: 9.8 (95% CI, 3.1-30.5)
- Median monthly consumption of peanut in infants 8-14 months old
 - Israel = 7.1 grams
 - UK = 0 grams

Learning about Early Introduction of Peanuts (LEAP) Study

- Protocol:
 - Infants 4-11 months of age
 - Moderate-to-severe eczema and/or egg allergy
 - All underwent skin prick test (SPT) and in office challenge
 - Randomized to two groups:
 - Consume 2 grams peanut 3 days/week until age 5
 - Peanut avoidance
 - Follow up oral challenge at 5 years of age

LEAP Study Outcomes

- Primary outcome
 - Proportion of participants with peanut allergy at 60 months of age determined by oral food challenge
- Secondary outcomes
 - Skin prick size
 - Various immunologic parameters
 - Safety

LEAP Study

- 640 infants randomized (median age 7.8 months)
 - 542 SPT negative
 - 98 SPT positive (1-4 mm wheal)
- Primary prevention = no sensitization
- Secondary prevention = sensitized, not allergic
- ****SPT > 5 mm excluded from study*
 - 95% confidence interval for likely clinical reaction = 8 mm for positive peanut allergy

LEAP Results

Access image: Du Toit G, et al. N Engl J Med. 2015 Feb
26;372(9):803-13.

Figure 2, Page 808.

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86% Reduction
Primary
Prevention

70% Reduction
Secondary
Prevention

Secondary Outcomes

- Safety
 - No deaths or difference in serious adverse events between two groups
- Skin prick wheal diameter
 - Significant increase in size from baseline in avoidance group
 - Differences between both groups at all time points
- Immunologic parameters
 - Peanut IgG and IgG4:IgE ratio higher in consumption group

Limitations of LEAP

- DO NOT try this at home for at risk infants!!!
- Not applicable to anyone already diagnosed with peanut allergy
- Not 100% effective
- Low risk infants not included in the study
- History of other food allergies not included
- Yet to be replicated in other populations
- Cannot extrapolate peanut feeding practices
 - Source
 - Duration
 - Amount

What's New?

- **Landmark** food allergy study
- Demonstrated that early introduction of peanut may protect against development of peanut allergy
- Prior opinion: avoidance prevents development of allergy
- Current data: early introduction induces tolerance
- This represents a HUGE paradigm shift!!!!

How Can this Change Practice?

- 2015 consensus recommendations endorsed by AAP
- NIH/NIAID guidelines forthcoming
 - Feed all infants peanut before 11 months of age
 - Risk stratification:
 - No eczema or other food allergy: feed without testing
 - Moderate-to-severe eczema and/or egg allergy:
 - Serum IgE < 0.35 kU/L = feed peanut
 - Skin prick test
 - 0-2 mm = feed peanut
 - 3-7 mm = physician supervised feeding
 - \geq 8 mm = likely allergic, avoid peanut

But Wait...There's More!

ORIGINAL ARTICLE

Effect of Avoidance on Peanut Allergy after Early Peanut Consumption

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Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the Immune Tolerance
Network LEAP-On Study Team*

LEAP-On

- Same participants/criteria from LEAP
- Enrolled 88.5% of participants (558 children)
- Primary outcome:
 - Development of peanut allergy at 6 years of age after 12 months of avoidance
- Adherence:
 - 90.4% in original peanut avoidance group
 - 69.3% in peanut consumption group

LEAP-On Results

- After 12 months of peanut avoidance:
 - No increase in peanut allergy from peanut consumption group:
3.6% at 5 years vs 4.8% at 6 years
 - Total of 3 new cases of peanut allergy in each group
 - Continued lower rates of peanut allergy in consumption group:
 - 4.8% vs 18.6%

What's New?

- LEAP-On demonstrates that early introduction of peanut prevents the development of allergy
- LEAP did not appear to induce long term desensitization
- How does this change practice?
- Confirms and reinforces LEAP findings

Fitting This into the Medical Home

- Discuss peanut introduction at 4 month well visit
- Incorporate other family members (especially those with peanut allergy) into shared decision making process
- Partner with a local allergist to help with referrals, skin prick testing, challenges

Poll # 2

- What is the most effective method at treating viral induced asthma exacerbations in young children?
 - Oral corticosteroids
 - Quadrupling dose of inhaled corticosteroids
 - Azithromycin
 - On demand use of leukotriene antagonists

Azithromycin for Lower Respiratory Tract Illnesses

Original Investigation

Early Administration of Azithromycin and Prevention of Severe Lower Respiratory Tract Illnesses in Preschool Children With a History of Such Illnesses A Randomized Clinical Trial

Leonard B. Bacharier, MD; Theresa W. Guilbert, MD; David T. Mauger, PhD; Susan Boehmer, MA; Avraham Beigelman, MD; Anne M. Fitzpatrick, PhD; Daniel J. Jackson, MD; Sachin N. Baxi, MD; Mindy Benson, MSN, PN; Carey-Ann D. Burnham, PhD; Michael Cabana, MD; Mario Castro, MD, MPH; James F. Chmiel, MD, MPH; Ronina Covar, MD; Michael Daines, MD; Jonathan M. Gaffin, MD, MMSc; Deborah Ann Gentile, MD; Fernando Holguin, MD; Elliot Israel, MD; H. William Kelly, PharmD; Stephen C. Lazarus, MD; Robert F. Lemanske Jr, MD; Ngoc Ly, MD; Kelley Meade, MD; Wayne Morgan, MD; James Moy, MD; Tod Olin, MD; Stephen P. Peters, MD; Wanda Phipatanakul, MD, MS; Jacqueline A. Pongracic, MD; Hengameh H. Raissy, PharmD; Kristie Ross, MD; William J. Sheehan, MD; Christine Sorkness, PharmD; Stanley J. Szefer, MD; W. Gerald Teague, MD; Shannon Thyne, MD; Fernando D. Martinez, MD; for the National Heart, Lung, and Blood Institute's AsthmaNet

Wheezing in Toddlers - Background

- Approximately 40% of toddlers wheeze at some point
 - 14-26% develop recurrent wheezing in first 6 years
- Viral and bacterial infections are most common trigger in this age group
- Ideal treatment strategies remain elusive
- Macrolide antibiotics have been investigated for asthma therapy
 - Anti-microbial vs anti-inflammatory effects?

Asthma Predictive Index

- Primary: ≥ 4 wheezing episodes per year
- Secondary:

At least 1 Major:

- Parental asthma
- Physician diagnosed eczema
- +IgE to at least aeroallergen

At least 2 Minor:

Wheezing apart from colds
Peripheral eosinophils $\geq 4\%$
+IgE to milk, egg, or peanut

Azithromycin for LRTIs

- Protocol
 - Children 12-71 months old
 - History of recurrent severe wheezing with lower respiratory tract infections (LRTIs)
 - Oral steroids
 - Unscheduled office visit
 - Urgent care/ED utilization
 - Exclusion criteria:
 - ≥ 5 courses systemic steroids in past 12 months
 - ≥ 2 hospitalizations in past 12 months
 - Use of controller medication for more than 8 months in past year

Azithromycin for LRTIs

- Protocol:
 - Double blind, parallel group trial; initially 52 wks → extended 78 wks
 - Azithromycin (12 mg/kg Qday x 5 days) vs placebo
 - Start at first onset of usual LRTI
 - All participants also received albuterol 4 times/day x 48 hours
- Primary outcome
 - Number of treated RTIs not progressing to severe LRTI (for anyone with at least one RTI) within 14 days
- Severe LRTI:
 - Moderate symptoms after 3 albuterol treatments over 1 hour
 - Needing albuterol more than every 4 hours
 - More than 6 albuterol treatments in 24 hours
 - Ongoing moderate-to-severe cough for 5 or more days since initiation of meds

Azithromycin for LRTIs

- Secondary outcomes
 - Number of urgent care, ED, hospitalizations
 - Asthma symptom and albuterol diaries
 - Culture data for resistant organisms

Results

Access image: Bacharier LB, et al. JAMA
2015;314(19):2034-44.

Table 1, Page 2037.

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Results

- 39.1% atopic
- 46.8% had + modified Asthma Predictive Index
- 937 RTIs occurred in 443/607 participants
 - 1.87 courses of azithromycin per participant year
- Viral pathogens detected (rhinovirus most common)
 - 83% of RTIs in azithromycin group
 - 80% of RTIs in placebo

Primary Outcome

- Azithromycin group had lower risk of progressing to severe LRTI
- Number Needed to Treat decreased with each RTI
 - 1 = 33
 - 2 = 14
 - 3 = 10
 - 4 = 7

Access image: Bacharier LB, et al.
JAMA 2015;314(19):2034-44.

Figure 2, page 2040.

Image removed due to copyright.

Potential Treatment-Effect Differences

Access image: Bacharier LB, et al. JAMA
2015;314(19):2034-44.

Figure 3, Page 2041.

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Secondary Outcomes

- Symptom severity
 - Decreased in treatment arm only in severe LTRIs
- No differences
 - Health care utilization (3.6% vs 5.4%)
 - Albuterol use
 - Time to 2nd RTI
 - Acquisition of azithro resistant organisms (16.7% vs 10.8%)
 - GI adverse effects

Bacharier LB, et al.
JAMA
2015;314(19):2034-
44.

Figure 4, Page 2042.
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to copyright.

What's New?

- Non-steroid intervention for common wheezing phenotype seen in primary care
- Azithromycin started at earliest sign of RTI was effective in reducing risk of severe LRTI
 - Irrespective of modified asthma predictive index
 - Well tolerated
- May represent a treatment option where current void exists
 - Oral steroids may not be effective in preschool wheezers

What Questions Remain?

- Mechanism of action?
- What about overuse of antibiotics?
 - Resistant pathogens
 - Alteration of microbiome
- Will this be effective in more persistent asthmatics?
- Can this be even more effective for recurrent severe LRTIs?
 - Participants who had a severe LRTI completed study and did not continue

Fitting This into the Medical Home

- Shared decision making with parents regarding best treatment options for wheezing
- Written treatment plans to be shared with daycare, schools
- Communication with specialists regarding patient referrals, treatment plans

Poll # 3

- A 12 yo patient complains of chronic abdominal pain, reflux, and intermittent emesis. You obtain a food IgE panel. Milk = 2.06 kU/L. What is your advice?
 - Remove milk from the diet
 - Rotational diet allowing milk every 4 days
 - Allergy referral
 - Not a milk allergy

Food Allergen Panel Testing

Food Allergen Panel Testing Often Results in Misdiagnosis of Food Allergy

J. Andrew Bird, MD¹, Maria Crain, CPNP², and Pooja Varshney, MD³

Sensitization \neq Allergy

- Sensitization
 - The detection of specific IgE toward an allergen through skin prick, intradermal, or serum specific IgE testing
- IgE mediated hypersensitivity
 - Characteristic clinical symptoms upon exposure to an allergen AND...
 - The detection of specific IgE toward that allergen

IgE Mediated Food Allergies

- Cow's milk, egg, soy, wheat, peanuts, tree nuts, fish, and shellfish account for > 90% of all food allergy
- Reactions are objective, immediate onset and reproducible with every exposure to the offending food, no matter what form
- Typical symptoms:
 - Urticaria
 - Angioedema
 - Emesis
 - Rhinorrhea
 - Wheezing
 - Hypotension
 - Anaphylaxis

Serum Specific IgE Testing

- The best test to determine whether someone is allergic to a food is ingestion of that food
- Specific IgE testing is best utilized to confirm a suspicious history
- Levels of IgE specific for food and/or inhalant allergens can be obtained through routine venipuncture

- Commercial panels widely available and marketed as excellent screening tools

- Results reported in a range from 0.1 kU/L – 100 kU/L
 - Also reported as arbitrary classes (1 through 5)

 - A big “!” will accompany any value reported > 0.35 kU/L

Specific IgE Cutoff Points

- Values differ by food
- Values only established for select number of foods
- The level does not equate to the severity of reaction
 - In general, the higher the level, the more likely it has clinical relevance

Specific IgE Cutoff Points

Access image: Sampson HA. JACI.
2001;107(5):891-6.

Table IV, Page 894.

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Food Allergen Panel Testing

- Single tertiary care referral center
- Retrospective review
 - All new patients seen between Sept 2011-Dec 2012
- Inclusion
 - Any patient who had a food specific IgE panel obtained by PCP
- Exclusion
 - Eosinophilic esophagitis
 - Missing results

Food Allergen Panel Testing

- Patients received comprehensive evaluation
- History consistent with IgE mediated reactions
- Skin testing if deemed necessary
 - 54.4% of encounters
- Repeat serum IgE testing if deemed necessary
 - 19% of encounters
- Oral food challenges
 - 99 total challenges in 81 patients (29.6%)

Results

- 797 new patient encounters
- 35% (284) had received a food allergy panel
- Of the 126 (45.9%) avoiding a food based upon PCP recommendations, 88.9% were able to reintroduce at least 1 new food into their diet

- Positive predictive value of panel testing = 2.2%

Results

- Only 32.8% (90) had a history warranting food allergy evaluation

Access image: Bird JA, Crain M, Varshney P. J Pediatr 2015;166(1):97-100.

Figure 2, Page 98.

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Reintroduction of Foods

Access image: Bird JA, Crain M, Varshney P. J
Pediatr 2015;166(1):97-100.

Figure 3, Page 99.

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Cost Analysis

Access image: Bird JA, Crain M, Varshney P. J
Pediatr 2015;166(1):97-100.

Table II, Page 99.

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What's New?

- One of few reports demonstrating clinical harm that occurs from overdiagnosis of food allergy based upon IgE testing
- Overuse of food specific IgE panels leads to unnecessary use of health care resources and increased cost

How Can This Change Practice?

- NO indication to order food specific IgE testing unless clinical history is consistent with IgE mediated reactions
- Rare, if any, occasion to obtain IgE panels
- Specific IgE results need to be interpreted within the clinical context and with understanding of how values differ by food and age
- Treat the patient, not the number!
 - Do not remove food from the diet if someone is eating without problems

Fitting This into the Medical Home

- Educated discussions with families regarding the utility of diagnostic testing
- Written communication with daycares, schools regarding food allergy diagnosis and management
- Provision of all relevant test results when referrals are placed for allergy evaluation

Poll # 4

- Your 12 month old patient has recurrent episodes of eczema that improve with topical steroids. Parents want to know the cause of their eczema. What test do you order?
 - Food specific IgE panel
 - Allergy testing for milk, egg, and peanut only
 - Inhalant IgE testing
 - None

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

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

Spergel JM, et al. Pediatrics 2015;136(6):1530-8.

Background

- Atopic dermatitis (AD) is a common condition presenting during infancy
- Children with AD are at increased risk for development of other allergic conditions
- Previous studies have demonstrated varying rates of IgE mediated food allergy in AD patients, 15-40%
 - Large Australian cohort, infants with AD at 12 months of age
 - 11 times more likely to have peanut allergy
 - 5.8 times more likely to have egg allergy

Background

- Due to co-morbidity of AD and food allergy, many families and PCPs attribute presence of or worsening AD to underlying food allergy
- Predictive values for food specific IgE levels have not been established in the setting of AD
- Current guidelines: Consider food allergy evaluation
 - Persistent AD in spite of optimal management
 - Reliable history of immediate reaction after ingestion of specific food

Specific IgE in Infants with Eczema

- Methods
 - Analysis performed of data from large Study of Atopic March study
 - Primary study: long term safety and efficacy of 1% pimecrolimus
- Inclusion
 - 3-18 months of age
 - Diagnosis of atopic dermatitis (prespecified criteria) for 3 months or less prior to enrollment
 - 1st degree relative with AD or allergies/asthma
- Exclusion
 - No other atopic conditions
 - No use of topical/systemic agents 7 days prior to 1st use of pimecrolimus

Methods

- 2 phases at 36 clinics
 - Phase 1: 36 month, Randomized Double Blind pimecrolimus vs placebo
 - Phase 2: Open label pimecrolimus for up to 33 months, or age 6
- AD severity assessed at every visit
- Food allergy diagnosed by point system
 - Symptoms, timing, suspected food
- Food sIgE obtained for top 8 allergens
 - Visit # 2, 14, and 20 (week 1, 3 years, 6 years)

Results

- 1091 patients randomized (1065 final Intention To Treat population)
- Mean age 7.3 month (± 3.9)
- 62.1% boys
- 68.8% caucasian
- 92.3% had mild-to-moderate atopic dermatitis

Results

- By end of Open Label phase, 15.9% developed food allergy
 - Peanut = 6.6%
 - Milk = 4.3%
 - Egg = 3.9%
 - Seafood, wheat, soybean < 0.5%
- Other conditions
 - Asthma = 10.7%
 - Allergic conjunctivitis = 14.1%
 - Allergic rhinitis = 22.4%

Specific IgE Levels and Food Allergy

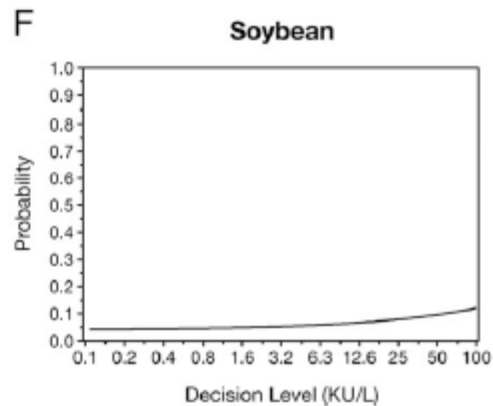
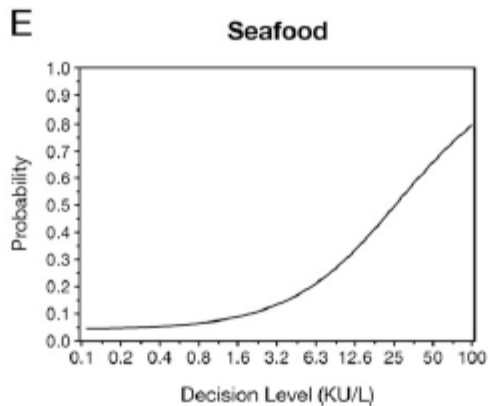
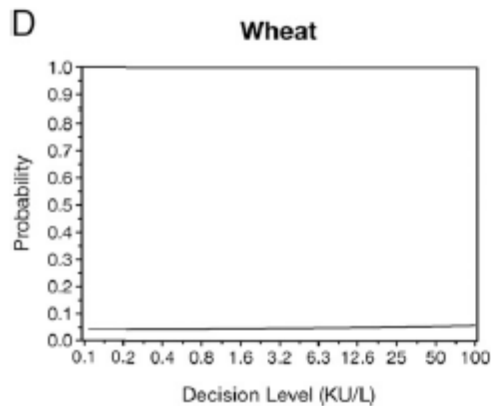
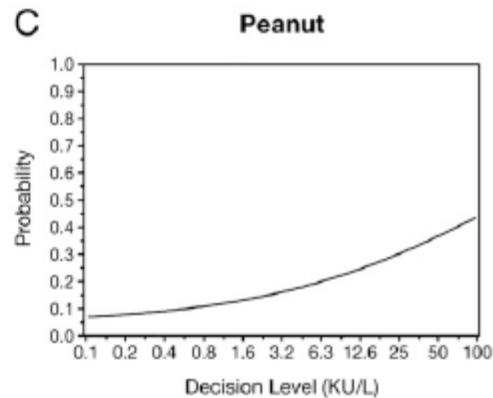
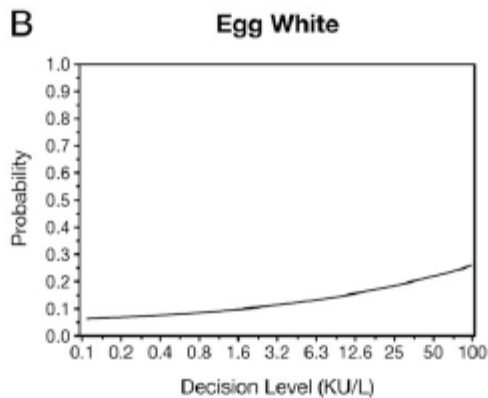
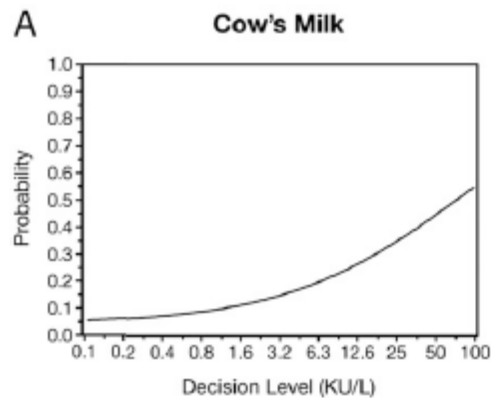


TABLE 4 Performance Characteristics of sIgE for Food Allergy

Food	IgE Cutoff, kU/L	Sensitivity	Specificity	PPV	NPV
Baseline					
Peanut	5	0.36	0.91	0.22	0.95
	14	0.19	0.95	0.20	0.94
Cow's milk	5	0.38	0.96	0.26	0.97
	15	0.24	0.98	0.30	0.97
Egg white	2	0.54	0.85	0.14	0.98
	7	0.20	0.92	0.10	0.96
Seafood mix	0.35	0.50	0.98	0.11	1.00
Wheat	0.35	0.33	0.86	0.01	1.00
Soybean	0.35	0.67	0.88	0.02	1.00
End of DB phase					
Peanut	5	0.62	0.89	0.43	0.95
	14	0.49	0.93	0.48	0.93
Cow's milk	5	0.42	0.97	0.41	0.97
	15	0.35	0.99	0.56	0.97
Egg white	2	0.45	0.86	0.16	0.96
	7	0.17	0.93	0.13	0.95
Seafood mix	0.35	1.00	0.90	0.06	1.00
Wheat	0.35	0.50	0.72	0.01	1.00
Soybean	0.35	0.67	0.77	0.02	1.00

What's New?

- Long term, prospective trial of food allergy in infants with atopic dermatitis
- Unlike other studies, enrolled all AD severities, no prior history of food allergy
- 15.9% lower than previously reported studies
- Peanut, milk, egg most common = same as other studies
- Decision points for PPV* differ from other studies
- Very low PPV observed for specific IgE

*PPV = positive predictive value

How Can This Change Practice?

- These results do not support the use of food specific IgE testing for infants with mild to moderate atopic dermatitis
- Consider food challenge as gold standard
- Do not prescribe food elimination diets on basis of sIgE levels alone
- Presence of IgE by itself has very low PPV, values may need to be much higher in atopic dermatitis

Fitting This into the Medical Home

- Informed and shared decision making with parents regarding the evaluation and management of atopic dermatitis
- Written and verbal education regarding daily skin care management for atopic dermatitis
- Provision of all relevant test results to specialists when referrals are placed

Thank You

