The Microbiome and Food Allergies

Presented by
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Overview

- Food allergy 101
  - Epidemiology, hygiene and tolerance
- Cohort studies indirectly suggesting a role for the microbiome
- Building the case for the importance of the microbiome
  - Association, Functional, Intervention (in progress)
- Why it matters and what the future may bring
  - ‘Sutton’s Law’, Prevention, Secondary Prevention and Treatment
- Questions
Food allergy 101: Epidemiology

- Jackson KD et al. National Child Health Services Data Brief #121; May 2013
- Liew WK et al. J Allergy Clin Immunol 2009; 123:434e42

Cooper, and higher than Sicherer et al.’s 20 national estimate of 1.4% in 2008. Although our data suggest that the burden of childhood peanut allergy has increased over the past decade, the authors of a recent study demonstrated that introducing peanut-containing foods alongside typical complementary foods between 4 and 11 months can achieve relative reductions in peanut allergy risk of up to 80% among high-risk infants. Consequently, the National Institute of Allergy and Infectious Diseases’ sponsored 2017 “Addendum Guidelines for the Prevention of Peanut Allergy” were released, which guide clinicians in promoting early peanut introduction for primary peanut allergy prevention. Therefore, if the “Prevention of Peanut Allergy” guidelines are broadly implemented, the age-specific peanut allergy prevalence estimates reported in this study may provide important baseline reference points for future work.

Although double-blinded placebo-controlled oral food challenges remain the current “gold standard” for FA diagnosis, such methods were not employed in the current study because of their expense, impracticality, and concerns about nonparticipation bias. As in past work to strengthen the rigor of our parent-reported questionnaire, stringent criteria were established in collaboration with an expert panel to exclude FAs where corresponding symptom report was not consistent with immunoglobulin E–mediated FA. Nevertheless, by relying exclusively on parent-report and not directly observing symptoms immediately after allergenic food protein consumption, misestimation of true FA prevalence and symptomatology remains possible. However, it is important to recognize the use of survey-based approaches given their ability to capture patients with FAs who may not receive formal evaluations or diagnoses.

CONCLUSIONS

These data suggest that childhood FA is a significant public health issue resulting in relatively high rates of severe allergic reactions and ED use. Previous findings of racial differences in FA prevalence were also supported here with elevated rates identified among non-Hispanic African American children. Overall, these findings provide critical epidemiologic information that improves understanding of the public health impact of childhood FA.

ACKNOWLEDGMENTS

We thank Michael Dennis, PhD, and Nada Ganesh, PhD, of NORC at the University of Chicago; Ozge Nur Aktas, MD, Lauren Kao, MA, and the members of our expert panel.

ABBREVIATIONS

CI: confidence interval
EAI: epinephrine autoinjector
ED: emergency department
FA: food allergy
OAS: oral allergy syndrome
OR: odds ratio
SSI: Survey Sampling International

In this contemporary cohort study of 7310 FIA-related ED visits in children younger than 18 years, the most frequent ED visits were among children younger than 3 years, followed by 3- to 6-year-olds. Over the 10-year study time frame, ED visits for pediatric FIA increased four-fold in adolescents aged 13-17 years (413%). Among specified foods, peanuts accounted for the highest rates of FIA-related ED visits, followed by tree nuts/seeds. To our knowledge, this is one of the first studies to provide a comprehensive analysis of FIA-related ED visits in US children by analyzing specific triggers and healthcare utilization outcomes among children in multiple age-groups.

We found increasing rates of FIA ED visits, in contrast to a study by Clark et al,13 who reported stable trends from 2000 to 2009. However, our findings agree with more recent data citing increases in FIA-related ED visits.14 Given that our study concerned rates from 2005 to 2014, the increase in FIA-related ED visits most likely represents a relatively recent change. The increasing rates of ED visits related to FIA may be due to a combination of factors, including an increasing prevalence of food allergy, an increased awareness of the diagnosis, and a lower threshold for seeking acute medical care.

In our cohort, whereas rates of FIA-related ED visits increased, overall proportions of inpatient and ICU admissions decreased. In a recently published study, Parlaman et al16 conducted a retrospective cohort study from 37 children’s hospitals from 2007 to 2012 and similarly did not find any increase in the proportion of ED patients hospitalized or admitted to the ICU despite increasing rates of FIA-related ED visits. These findings suggest that most pediatric FIA ED cases are self-limited and do not require routine hospital admission. This agrees with guidelines that advise the observation period be individualized on the basis of factors that include reaction severity, access to care, and patient reliability.

Future studies examining FIA-related ED outcomes are necessary to ensure proper healthcare delivery. The decrease in proportions of inpatient and ICU admissions is likely due to increased utilization of ED observation units or inpatient observation status. In their study, Parlaman et al16 did not examine rates of patients sent to observation units. Although not specifically demonstrated in that study, the important role of observation units in managing anaphylaxis has been highlighted in other studies. In a study in an Australian pediatric ED, Braganza et al18 reported results similar to ours: 39% of children were observed in an observation unit, compared with 7% who were admitted to a general ward.
Hay fever, hygiene, and household size

David P Strachan

Hay fever has been described as a “post industrial revolution epidemic,” and successive morbidity surveys from British general practice suggest that its prevalence has continued to increase over the past 30 years. Other evidence suggests a recent increase in the prevalence of asthma and childhood eczema. This paper suggests a possible explanation for these trends over time.

“Over the past century declining family size, improvements in household amenities, and higher standards of personal cleanliness have reduced the opportunity for cross infection in young families.”

Humoral immune regulation in response to allergens

Few studies have addressed the effects of a Western lifestyle and chronic infections on humoral immunity. Healthy or 'tolerant' individuals often produce high amounts of allergen-specific IgG4 and/or IgA, and IgA-deficient individuals are at risk of developing an allergy51. Recently, it was shown that children who respond to allergens with a positive serum IgE count but a negative skin test have higher titers of allergen-specific IgG, which suggests that the presence of IgG can suppress tissue inflammation caused by allergens 41. This reduced skin-test reactivity to allergens is also seen in helminth-infected allergic children. Through polyclonal expansion of IgE-secreting B cell populations, helminth infections increase the total serum IgE concentration, which might increase competition with allergen-specific IgE for binding to the high-affinity receptors on mast cells and basophils52. Helminth infections also induce high concentrations of IgG4, which can intercept an allergen before it binds to IgE and can cross-link the inhibitory receptor Fc GRIIb, shutting down Fc ERI signaling and thus reducing skin-test reactivity and clinical symptoms of allergy 41,53,54. Recent protein-sequence analyses have shown that a large number of allergens have linear and conformational epitopes that are highly similar to helminth-derived proteins 55,56. Chronic exposure to these cross-reactive antigens in helminth-infected people may, in the long run, lead to tolerance, similar to what is observed with allergen immunotherapy, which is also associated with IgG4 responses 57.

Allergen cross-reactive antibodies directed to selected microbes of the gut and lung microbiome have also been described recently. An antibody to A-1,3-glucan-bearing Enterobacter cloacae was shown to cross-react with the cockroach allergen Bla g 2. Neonatal, but not adult, mice immunized with E. cloacae were protected from cockroach-induced asthma, and this protection was found to depend on IgA-producing plasma cells that accumulated in the lungs 58. HDM allergen contains phosphorylcholine (PC) epitopes shared with PC of Streptococcus pneumoniae. Neonatal mice immunized with formalin-inactivated PC-bearing S. pneumoniae were found to be protected from HDM-driven asthma, and this response was dependent on the presence of PC in the bacterium and accumulation of PC-specific B cells in the lungs. PC-specific antibodies were able to block the uptake of HDM allergen by DCs and subsequent induction of T H2 cell immunity in vitro and in vivo 59. Along the same lines, antibodies cross-reactive to polysaccharides on group A streptococci, as well as immunization with these streptococci, suppress respiratory allergy to chitin and Aspergillus spores in neonatal mice 60. Strikingly, all of

- Mode of delivery
- Maternal diet
- Maternal antibiotics
- Family size
- Sibship order
- Daycare attendance
- Breast milk
- Skin microbiome
- Nasopharynx microbiome
- Lung microbiome
- Gut microbiome
- 'Time window'
- Organ development
- Immune system development
- Infant formula
- Raw cow's milk
- Infection history
- Antibiotic use
- Vaccination
- Close contact with pets and farm animals
- www.foodallergy.org
- MICROBIOME: The sum of microbes and their genomic elements in a particular environment.
- SHORT-CHAIN FATTY ACID: Fatty acids with fewer than 6 carbon atoms.
- RORγ+ Treg CELLS: Also referred to as type 3 regulatory T (Treg) cells, these Foxp3+ Treg cells are generated in response to the intestinal microbiota and are essential for suppression of type 2 immunity.
- PROBIOTIC: Live microorganisms with beneficial effects on the host.
- PREBIOTIC: Nondigestible substrates that promote the growth, function, or both of beneficial microorganisms.
- DYSBIOSIS: A state of imbalance in a microbial ecosystem.
Food allergy 101: The tolerance paradigm


www.foodallergy.org
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Observational cohort studies (allergy generally)

- Prenatal maternal exposure to pets
- Birth by vaginal versus cesarean section delivery
- Growing up in rural environment (close contact with animals)
- Growing up with pets (or older siblings)

Observational cohort studies specific to food allergy

Observational cohort studies specific to food allergy

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th></th>
<th>Adjusted¹</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.79 (0.65, 0.96)</td>
<td>0.018</td>
<td>0.81 (0.65, 1.00)</td>
<td>0.052</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>0.54 (0.32, 0.91)</td>
<td>0.021</td>
<td>0.52 (0.30, 0.92)</td>
<td>0.025</td>
</tr>
<tr>
<td><strong>Number of siblings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>0.74 (0.60, 0.93)</td>
<td>0.72 (0.57, 0.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two</td>
<td>0.62 (0.44, 0.86)</td>
<td>0.56 (0.38, 0.81)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three or more</td>
<td>0.32 (0.15, 0.65)</td>
<td>0.31 (0.14, 0.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Per sibling</strong></td>
<td>0.75 (0.66, 0.85)</td>
<td>&lt;0.001</td>
<td>0.72 (0.62, 0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cat ownership</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cat</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Cat outside only</td>
<td>0.79 (0.45, 1.41)</td>
<td>0.43</td>
<td>0.93 (0.49, 1.77)</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Cat allowed inside</strong></td>
<td>0.62 (0.45, 0.85)</td>
<td>0.004</td>
<td>0.75 (0.52, 1.09)</td>
<td>0.13</td>
</tr>
<tr>
<td>Dog ownership¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No dog</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Dog outside only</td>
<td>0.77 (0.55, 1.08)</td>
<td>0.13</td>
<td>1.09 (0.75, 1.57)</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>Dog allowed inside</strong></td>
<td>0.55 (0.41, 0.73)</td>
<td>&lt;0.001</td>
<td>0.72 (0.52, 0.99)</td>
<td>0.043</td>
</tr>
<tr>
<td>Age at first introduction of egg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–6 months</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>7–9 months</td>
<td>1.11 (0.84, 1.46)</td>
<td>1.03 (0.77, 1.39)</td>
<td></td>
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</tr>
<tr>
<td>10–12 months</td>
<td>1.30 (0.98, 1.73)</td>
<td>&lt;0.001</td>
<td>1.28 (0.95, 1.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>4.87 (3.30, 7.18)</td>
<td>&lt;0.001</td>
<td>4.36 (2.84, 6.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Immediate family (parent/s or)</td>
<td>1.58 (1.26, 1.99)</td>
<td>&lt;0.001</td>
<td>1.82 (1.40, 2.36)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Prospective Observational Infant Cohort Study  
n=1003
and survival analyses, P values for significance were calculated using the Wald test, with a priori levels of significance set at P < .05. Group comparisons were performed using c2, Mann-Whitney U, and Kruskal-Wallis rank sum tests of significance as appropriate.

Sensitivity analysis was performed by repeating the logistic regression analyses to assess alterations in the primary and secondary outcomes specified above when combining the questionable FPIAP cases with the FPIAP cases.

RESULTS
Characteristics of the GMAP cohort
Of the 1162 infants approached, 1003 (86%) enrolled in the GMAP study (Figure 1). After exclusion of siblings, subjects with inadequate data through 6 months, and FPIAP cases not meeting research criteria, 903 infants were included in the final analysis (Figure 1). Over the course of the study, 80 (9%) infants withdrew participation, 55 (69%) of whom relocated or left the pediatrics practice and 25 (31%) of whom chose to no longer participate. We found no statistically significant differences between infants who withdrew before 6 months and the remainder of the cohort across any of our exposures of interest (not shown).

Of the main cohort of 903 infants, most were white, with a slight male predominance (Figure 2). Most were born at term (89%), delivered vaginally (68%), and 50% were exposed to intrapartum maternal antibiotics, whereas a small proportion (9%) were directly exposed to antibiotics postnatally (Figure 2). The median age at enrollment was 8 days (interquartile range [IQR], 5-14). At their first pediatrics visit, most infants (62%) were being fed only breast milk, 7% only formula, and 32% a mixed diet (both breast milk and cows milk-based formula).

Forty-seven percent were first-born children and 41% had pets living in their home at birth; 45% had first-degree family members with atopic diseases and 15% had first-degree relatives with food allergies.

Cumulative incidence of FPIAP
Of the 903 healthy infants included in the final analysis, 169 of them were diagnosed with FPIAP and 153 met the predefined inclusion criteria (Figure 1). This identifies a cumulative incidence of FPIAP of 17% over 3 years in this healthy unselected population. The median age at symptom onset was 26 days (IQR, 14-34) and the median age at FPIAP diagnosis was 35 days (IQR, 26-81).

Risk factors for FPIAP development
A family history in a first-degree relative of food allergy (odds ratio [OR], 1.9; 95% confidence interval [CI], 1.2-2.8; P = .005), bloody stools (OR, 4.5; 95% CI, 2.7-7.4; P < .001), and diet intolerance (OR, 3.5; 95% CI, 2.3-5.4; P < .001) were risk factors for the development of FPIAP, all of which were assessed...
Initial Diet

Proportion with FPIAP

Hazard Ratios [95% CI], p-value

B v. F: 0.47 [0.26, 0.86], p=0.0140
M v. F: 0.39 [0.20, 0.75], p=0.0051
M v. B: 0.82 [0.52, 1.29], p=0.3900

Number at risk

Formula 59
Breastmilk 558
Mixed 286

Age (months)

Diet over Time

Proportion with FPIAP

Hazard Ratios [95% CI], p-value

B v. F: 0.63 [0.40, 0.98], p=0.0398
M v. F: 0.44 [0.24, 0.78], p=0.0054
M v. B: 0.62 [0.38, 1.00], p=0.0497

Number at risk

Formula 59
Breastmilk 558
Mixed 286

Age (months)

Observational cohort studies: GMAP

- Milk (n=9): OR=6.3 [1.7, 23.7], p=0.007
- Egg (n=28): OR=2.4 [1.1, 5.4], p=0.034
- Peanut (n=28): OR=1.7 [0.7, 4.0], p=0.253

Unadjusted Odds Ratio [95% Confidence Interval]
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GUT MICROBIOTA ARE ASSOCIATED WITH THE CLINICAL TRAJECTORY OF FOOD ALLERGY

Sequencing-based studies of gut microbiota in children with food allergy have shown that gut microbiome composition is associated with the clinical trajectory of food allergy, and the timing of host-microbe interactions in early life appears to be important. The gut microbiome changes during the course of life, with the most rapid changes occurring in early life.

To examine the relationship between the infant gut microbiome and the clinical course of food allergy, investigators studied 226 infants with milk allergy (strictly defined based on OFC results, a convincing history, and positive allergy test results or flare of atopic dermatitis associated with milk ingestion and milk sIgE level >5k UA/L) from the multicenter Consortium for Food Allergy Research, whose clinical courses were followed longitudinally up to age 8 years. The investigators found that taxa from the Firmicutes phylum, including Clostridia, were enriched in the gut microbiome of infants with milk allergy age 3 to 6 months whose milk allergy later resolved by age 8 years, whereas this was not the case in infants with milk allergy of the same age who continued to have persistent milk allergy.

Based on these results, it is possible that (1) early infancy (ie, age 3-6 months) is a specific developmental window during which gut microbiota can shape the course of food allergy, and gut microbiota at later ages (eg, >6 months age) have little to no effect on food allergy course; and/or (2) gut microbiome composition might be associated with food allergy course later in life as well, but factors that appear during these older ages obscure this signal.

Separately, a study of 56 Japanese infants found evidence that the gut microbiota at age 2 months is associated with the development of self-reported food allergy by age 2 years. Specifically, among 14 infants with egg, cow’s milk, soy, and/or wheat allergy based on questionnaire by age 2 years, the investigators found that the genera Leuconostoc, Weissella, and Veillonella were underrepresented in their fecal samples compared to 27 of their counterparts who did not develop any food allergies by age 3 years.

We note that although self-reported and/or questionnaire-based assessments of food allergy are often used in studies of food allergy, they are limited by the likelihood of reporting inaccuracy, and supervised oral challenge–based assessments of food allergy remain the gold standard for accurate diagnosis.

Observational Analysis Intervention

Diet

Fecal Microbial Transfer

Probiotics

Prebiotics

Synbiotics

Healthy Food Allergic

Resistant Susceptible

Microbial Composition

FIG 1. Pathways to the development of microbial therapeutics for food allergy. Evidence for an important contribution of the gut microbiota to the pathogenesis of food allergy is derived from observational studies of distinct microbial composition in allergic and healthy human cohorts, and in mice with susceptibility versus resistance to food allergy. Evidence that changes in microbial composition lead to meaningful changes in host immunity come from studies using FMT into germ-free mice with susceptibility to food allergy. Additional functional evidence can be derived from in vitro culture systems examining the effect of stool extracts on immune phenotype. Based on the weight of this preclinical evidence, clinical trials using defined microbial transfer, probiotics, prebiotics, synbiotics, and FMT are in process to determine the efficacy of microbial therapeutics for the treatment of food allergy.

Egg allergy and egg sensitization


<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All subjects (n = 141)</th>
<th>Egg allergy (n = 66)</th>
<th>Controls (n = 75)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex — female</td>
<td>46 (32.6%)</td>
<td>19 (28.8%)</td>
<td>27 (36.0%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Age — Mo</td>
<td>9.7 (3.4)</td>
<td>11.7 (2.8)</td>
<td>7.9 (2.8)</td>
<td>$4.5 \times 10^{-13}$</td>
</tr>
<tr>
<td>Race — Caucasian</td>
<td>103 (73.0%)</td>
<td>47 (71.2%)</td>
<td>56 (74.7%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Egg sIgE (kUa/L)</td>
<td>3.4 (5.9)</td>
<td>5.3 (7.6)</td>
<td>1.7 (3.2)</td>
<td>$5.3 \times 10^{-4}$</td>
</tr>
<tr>
<td>Egg SPT (wheel mm)</td>
<td>7.0 (4.3)</td>
<td>8.4 (4.0)</td>
<td>5.7 (4.2)</td>
<td>$1.8 \times 10^{-4}$</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>None</td>
<td>7 (5.0%)</td>
<td>6 (9.1%)</td>
<td>1 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>25 (17.7%)</td>
<td>16 (24.2%)</td>
<td>9 (12.0%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>70 (49.6%)</td>
<td>27 (40.9%)</td>
<td>43 (57.3%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>39 (27.7%)</td>
<td>17 (25.8%)</td>
<td>22 (29.3%)</td>
<td></td>
</tr>
<tr>
<td>Currently breastfeeding</td>
<td>55 (39.0%)</td>
<td>16 (24.2%)</td>
<td>39 (52.0%)</td>
<td>$9.7 \times 10^{-4}$</td>
</tr>
<tr>
<td>Mode of delivery — vaginal</td>
<td>96 (68.1%)</td>
<td>44 (66.7%)</td>
<td>52 (69.3%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Solid food intake</td>
<td>127 (90.1%)</td>
<td>65 (98.5%)</td>
<td>62 (82.7%)</td>
<td>$1.5 \times 10^{-3}$</td>
</tr>
<tr>
<td>Antibiotics — any during lifetime</td>
<td>88 (62.4%)</td>
<td>50 (75.8%)</td>
<td>38 (50.7%)</td>
<td>$2.9 \times 10^{-3}$</td>
</tr>
<tr>
<td>Resolution of egg allergy by age 8 y</td>
<td>n/a</td>
<td>40 (60.6%)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Number (%) or mean (SD) reported.

*Fisher’s exact test for categorical variables, t test for continuous variables.
Egg allergy and egg sensitization


www.foodallergy.org
The IL4raF709 OVA model

Persistent vs transient milk allergy

No associations with mode of delivery, antibiotics, breast-feeding, AD

Persistent vs transient milk allergy

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Food allergic infants: human to murine model

- 56 infants with food allergy*
- 98 age-matched non-allergic controls
- Sampled at multiple timepoints from 1 to 30 months
- 16S but with higher resolution OTU picking
- Functional studies by fecal transplantation

* ‘to at least one of the major food allergens including milk, soy, egg, tree nuts, fish, shellfish, wheat, or peanuts’

- 4 infants with milk allergy
- 4 age-matched non-allergic controls
- Sampled once during infancy

- 16S but with high resolution OTU picking
- Functional studies by fecal transplantation

Food allergic infants: human to murine model number 2


www.foodallergy.org
Hierarchy of Evidence

- **Probiotics for Cow’s Milk Allergy**
  - 119 infants with CMA, *L. casei* and *B. lactis* did not accelerate tolerance
  - 55 infants with EHCF and *L. rhamnosus* GG (LGG) did resolve sooner
  - 220 infants with EHCF and LGG resolved CMA at higher rates during follow up to 3 years
  - Response associated with changes in frequency of butyrate producing organisms

- **LGG as adjuvant to peanut OIT (Tang et al):** at 4 years follow up, 67% v 4% actively consuming peanut
  - Larger follow up study with OIT alone arm in progress

Clinical trials

- NCT02960074 Boston Children’s Hospital, Rima Rachid
- NCT03936998 MGH-Vedanta Biosciences, Wayne Shreffler

Discovery Centers

Conduct novel research on treatments, diagnostics, prevention and improvements to care

- Boston FARE Clinical Network Discovery Center
  - MGH Brigham
  - Boston Children’s Hospital

https://www.foodallergy.org/resources/fare-clinical-network-centers-distinction
T_{reg} induction by a rationally selected mixture of Clostridia strains from the human microbiota


Clinical trials: NCT03936998

VE416 Phase Ib/II in Peanut Allergy - Plan Final

**Phase Ib**

- **Active** (10)
  - Vanc x5d
  - VE416 x 6 wks
- **Placebo** (10)
  - PBO x 6 wks

**Phase II**

- **Cohort 1** (10)
  - VE416 (143 mg)
- **Cohort 2** (10)
  - Vanc x5d
  - VE416 (143 mg)
  - PNOIT
  - PBO
- **Cohort 3** (10)
  - VE416 (143 mg)
- **Cohort 4** (10)
  - PBO

**Post-Phase II Maintenance**

- **DBPCFC1 (5030 mg)**
- **DBPCFC2 (5030 mg)**

**Entry DBPCFC**

- Age 12-55*
- Vanc x5d
- VE416 x 6 wks

**Inclusion**

- <100 mg VE416 + PNOIT

**Step Dose** (mg)

<table>
<thead>
<tr>
<th>Step</th>
<th>Dose (mg)</th>
<th>Sum Dose (mg)</th>
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<tr>
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</table>

**Post Phase II Maintenance**

- **PNOIT maintenance (40 mg)**
- **VE416**

**Inclusion:** tolerates at least 300 mg (430 mg cumulative) (randomized 1:1)

**Step Dose** (mg)

<table>
<thead>
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<td>2030</td>
</tr>
<tr>
<td>6</td>
<td>3000</td>
<td>5030</td>
</tr>
</tbody>
</table>

**Inclusion:**

- PNOIT: 300 mg daily
- Ad lib: 1 peanut at least three times a week

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* Extension of inclusion down to age 12 after interim safety review

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Wait! What about the skin??

EAACI Congress 2020 goes digital!
Bridging Innovations into Allergy and Asthma Prevention
EAACI.org 6-8 June 2020

#1412 - Longitudinal trajectories of eczema severity, duration, and affected body-region predict risk of food allergy in combination with filaggrin gene mutations

Ylescupidez, Alyssa / Du Toit, George / Salavoura, Katerina / Brough, Helen / Radulovic, Suzana / Bahnson, Henry T / Lack, Gideon

Staph, Staph, Staph (?)
Basic mucosal immunology and food science

- The mechanisms of sensing the diet are complex and poorly understood with myriad sensors utilized by specialized epithelial cells, immune cells and neuronal cells all likely sensing both bioactive components of food and metabolites of the microbiome

- Non-IgE-mediated food allergies, such as FPIES, EoE and FPIAP

- Role of microbiome in shaping the immune repertoire and metabolizing food proteins

- Impact of OIT on microbiome and relationship to outcomes

- Much more to come!!
The most obvious intervention would seem to be the one that is most likely to address the tolerance paradigm

Prevention, Secondary Prevention and Treatment
Evidence of Treg induction by OIT to food Ag


Overview

- Food allergy 101
  - Epidemiology, hygiene and tolerance
- Cohort studies indirectly suggesting a role for the microbiome
- Building the case for the importance of the microbiome
  - Association, Functional, Intervention (in progress)
- Why it matters and what the future may bring
  - ‘Sutton’s Law’, Prevention, Secondary Prevention and Treatment
- Questions
Evidence of Treg induction by OIT to food Ag – or not?


A key role for neutralizing antibodies

Thank you and acknowledgments

- Citations throughout – recommend recent review by Bunyanavich and Bern, JACI Dec 2019
- Research support from:
  - NIAID/CoFAR, Demarest Lloyd Foundation, Gerber Foundation, Food Allergy Science Initiative, EAT, Vedanta Biosciences
- Key collaborators:
  - MIT/FASI: Chris Love
  - MGH: Sarita Patil, Qian Yuan, Tori Martin, Yamini Virkud, Robert Anthony
  - FARE Discovery Center: Rima Rachid, Chen Rosenberg, Joyce Hsu
Question & Answer
YOUR Food Allergy Story Drives Research Forward

The FARE Patient Registry connects people living with food allergies to researchers seeking answers.

Join in 3 easy steps:

1. Enroll for free
2. Create your confidential patient profile
3. Take our surveys

JOIN TODAY at FAREregistry.org
Thank you!