Delayed Introduction and Less Frequent Egg Intake in Infancy and Increased Egg Allergy in Childhood

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PGY-4 - Allergy Immunology

Nov 7, 2021

Conflict of Interest/Disclosure

- This study was funded by the Egg Nutrition Center/American Egg Board. The funders had no role in data analysis, manuscript writing or the decision to submit it for publication.
- The authors have no other conflict(s) of interest to declare
**Background**

- Egg allergy is the second most common food allergy in infancy and childhood, affecting 0.5-2.5% of children (Dunlop, 2018) (Rona, 2007).
- Historically, recommendations existed to delay introduction of allergens such as egg in infant diets (AAP Committee on Nutrition, 2000).
- New evidence shows that early allergenic food introduction followed by consistent, frequent feedings is protective against the development of allergy to that food (Du Toit, 2015) (Perkin et al., 2016).
- The optimal timing of egg introduction and frequency of egg ingestion in an infant’s diet requires clarification (Greer et al., 2019).

**Theoretical Model**

- Environmental Food Exposure Hypothesis of Food Allergy Sensitization
HL3 I can't see anything on this slide. Should we combine with next slide or are there images to add?
Heather Lehman, 9/13/2021
Objectives

EXPOSURE
Egg Intake

Egg Introduction AGE
<2m, 3m, 4m, 5m, 6m, 7m, 9m, 10m, 12m

Egg FREQUENCY of Intake
Never, <1x/week, 2–4x/week, daily, ≥2x/day

OUTCOME
Egg Allergy

Egg Allergy in infancy → Persistence of Egg Allergy in Childhood

Methods

EXPOSURE
Egg Consumption in Infancy

Pregnant Mother
Prenatal Questionnaire
<2m, 3m, 4m, 5m, 6m, 7m, 9m, 10m, 12m

Monthly Survey

OUTCOME
Egg Allergy

0.6% (14/2377)
1yo EGG ALLERGY

0.9% (13/1379)
6yo EGG ALLERGY

No Egg Allergy
### Results

**Table 1.** Participant characteristics of all children and characteristics according to child delayed egg introduction beyond 12 months*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Children with introduction of eggs at 12m</th>
<th>Children with introduction of eggs delayed beyond 12m</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1050</td>
<td>N=709</td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>897 (85.4)</td>
<td>628 (88.6)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>41 (3.8)</td>
<td>19 (2.7)</td>
<td>0.2395</td>
</tr>
<tr>
<td>Hispanic</td>
<td>65 (6.2)</td>
<td>33 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Asian/Pacific Islander/Other</td>
<td>47 (4.5)</td>
<td>29 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Maternal Education Highest Level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highschool</td>
<td>198 (19.3)</td>
<td>98 (14.4)</td>
<td></td>
</tr>
<tr>
<td>College 1-3 years</td>
<td>381 (37.2)</td>
<td>230 (33.6)</td>
<td>0.653</td>
</tr>
<tr>
<td>College Graduate</td>
<td>329 (32.1)</td>
<td>261 (36.9)</td>
<td></td>
</tr>
<tr>
<td>Post Graduate</td>
<td>114 (11.1)</td>
<td>100 (14.7)</td>
<td></td>
</tr>
<tr>
<td>Maternal Employment Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>376 (34.9)</td>
<td>233 (32.23)</td>
<td>0.2427</td>
</tr>
<tr>
<td>Employed</td>
<td>700 (65.1)</td>
<td>490 (67.77)</td>
<td></td>
</tr>
<tr>
<td>Health Insurance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>48 (4.5)</td>
<td>31 (4.28)</td>
<td>0.9069</td>
</tr>
<tr>
<td>Yes</td>
<td>1,029 (95.5)</td>
<td>693 (95.72)</td>
<td></td>
</tr>
<tr>
<td>Breastfeed Ever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>124 (11.5)</td>
<td>120 (16.57)</td>
<td>0.0025</td>
</tr>
<tr>
<td>Yes</td>
<td>954 (88.5)</td>
<td>604 (83.43)</td>
<td></td>
</tr>
<tr>
<td>Daycare attendance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9m - No</td>
<td>277 (66.8)</td>
<td>187 (66.08)</td>
<td>0.8705</td>
</tr>
<tr>
<td>9m - Yes</td>
<td>138 (33.3)</td>
<td>96 (33.92)</td>
<td></td>
</tr>
<tr>
<td>Mother Egg Diet Changed During pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ate more</td>
<td>92 (16.7)</td>
<td>32 (9.04)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Ate less</td>
<td>35 (6.4)</td>
<td>27 (7.63)</td>
<td></td>
</tr>
<tr>
<td>Ate the same amount</td>
<td>416 (75.5)</td>
<td>272 (76.84)</td>
<td></td>
</tr>
<tr>
<td>Did not eat before or now</td>
<td>8 (1.5)</td>
<td>23 (6.60)</td>
<td></td>
</tr>
</tbody>
</table>

*Egg Allergy in infancy, Persistence of Egg Allergy in Childhood

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**Diagram:**

- **Exposure:** Egg Intake
  - Egg Introduction AGE
    - <2m, 3m, 4m, 5m, 6m, 7m, 9m, 10m, 12m
  - Egg FREQUENCY of Intake
    - Never, <1x/week, 2–4 x/week, daily, ≥2x/day

- **Outcome:** Egg Allergy
  - 1y, 6y
  - Egg Allergy in infancy, Persistence of Egg Allergy in Childhood
Delayed Introduction and Less Frequent Egg Intake in Infancy and Increased Egg Allergy in Childhood

Results

- Delayed egg introduction beyond 12 months was associated with egg allergy at 6 years.
- No significant difference in egg allergy at specific age of introduction <12 months.

<table>
<thead>
<tr>
<th>Total Population N</th>
<th>Children with Egg Allergy at 6 years n (% Total Population)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg not introduced by 2m</td>
<td>1378</td>
<td>13 (0.91)</td>
</tr>
<tr>
<td>Egg introduced by 2m</td>
<td>1</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Egg not introduced by 3m</td>
<td>1314</td>
<td>12 (0.91)</td>
</tr>
<tr>
<td>Egg introduced by 3m</td>
<td>2</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Egg not introduced by 4m</td>
<td>1289</td>
<td>10 (0.79)</td>
</tr>
<tr>
<td>Egg introduced by 4m</td>
<td>5</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Egg not introduced by 5m</td>
<td>1282</td>
<td>12 (0.91)</td>
</tr>
<tr>
<td>Egg introduced by 5m</td>
<td>7</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Egg not introduced by 6m</td>
<td>1224</td>
<td>11 (0.91)</td>
</tr>
<tr>
<td>Egg introduced by 6m</td>
<td>18</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Egg not introduced by 7m</td>
<td>1152</td>
<td>11 (0.91)</td>
</tr>
<tr>
<td>Egg introduced by 7m</td>
<td>62</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Egg not introduced by 8m</td>
<td>1033</td>
<td>10 (0.90)</td>
</tr>
<tr>
<td>Egg introduced by 8m</td>
<td>164</td>
<td>1 (0.01)</td>
</tr>
<tr>
<td>Egg not introduced by 10m</td>
<td>798</td>
<td>10 (0.13)</td>
</tr>
<tr>
<td>Egg introduced by 10m</td>
<td>319</td>
<td>1 (0.00)</td>
</tr>
<tr>
<td>Egg not introduced by 12m</td>
<td>472</td>
<td>9 (0.19)</td>
</tr>
<tr>
<td>Egg introduced by 12m</td>
<td>682</td>
<td>2 (0.03)</td>
</tr>
</tbody>
</table>

EXPOSURE
Egg Intake

Egg Introduction AGE
<2m, 3m, 4m, 5m, 6m, 7m, 8m, 9m, 10m, 12m

Egg FREQUENCY of Intake
Never, <1x/week, 2-4 x/week, daily, ≥2x/day

OUTCOME
Egg Allergy

Clinical Egg Allergy
Persistence of Egg Allergy in Childhood
Delayed Introduction and Less Frequent Egg Intake in Infancy and Increased Egg Allergy in Childhood

Results

- More frequent egg consumption at 4-10 months was associated with decreased egg allergy at 1 year

![Graph showing the relationship between age and egg allergy](image)

**EXPOSURE**

Egg Intake

- Egg Introduction
- Egg Frequency of Intake: Never, <1x/week, 2-4 x/week, daily, ≥2x/day

**AGE**

<2m, 3m, 4m, 5m, 6m, 7m, 8m, 10m, 12m

**OUTCOME**

Egg Allergy

- Clinical Egg Allergy
- Persistence of Egg Allergy in Childhood
Add mean to title of Y axis?
25192, 9/13/2021
Results

- More frequent egg consumption at 5, 6, 7, 10, and 12 months was associated with decreased egg allergy at 6 years.

Limitations

- Sample size of patients with egg allergy is small
  - n=14 at 1y; 0.6% of all patients
  - n=11 at 6y; 0.8% of all patients
- Egg allergy diagnosis only available as reported by parent stating “baby diagnosed as allergic to egg” on survey
  - Gold standard is office-based food challenge
- Potential narrow variation in some confounders due to mostly middle-high SES and white race of infants in IFPS
- Low rates of egg introduction through 9 months may limit ability to detect significance of introduction and frequent ingestion at early timepoints on childhood egg allergy.
LH3  isn't it just 5, 6, 7, 10, and 12 months that were significant for 6 years?
Lehman, Heather, 9/9/2021

23  Yes - not 4 months
25192, 9/13/2021

24  I will edit that
25192, 9/13/2021

HL1  It still shows an asterix over 4 months on the figure. You could just put a white box over that to hide it if you don't want to redo the figure.
Heather Lehman, 9/13/2021

Slide 14

LH5  11 or 13 patients with egg allergy at 6 years?
Lehman, Heather, 9/9/2021

25  Total we have 13 (demographic info on 13 patients) but with information on frequency is 11 - should I keep this at 13?
25192, 9/13/2021

HL2  Yes, keep N of 13. Mention in the frequency results slide that you only had frequency data on 11 of 13.
Heather Lehman, 9/13/2021
Conclusions

• Parent-reported egg allergy is significantly higher at 6 years old in children that delayed initial introduction of egg until 12 months or later

• The frequency of egg intake at 10 months old significantly impacts egg allergy development at age 1 year, the relationship persists at age 6 years

• This pediatric birth cohort suggests that increased frequency of egg intake in infancy is associated with decreased egg allergy in childhood.

Implication and Next Steps

• Frequent ingestion of egg in infancy is associated with egg tolerance in childhood.

• Delayed egg beyond 12 months is associated with egg allergy in childhood

• We encourage further research, in diverse cohorts, to investigate socio-demographic differences and optimal timing of egg introduction
Acknowledgements

- Infant Feeding Practices Study II (IFPS II) study participants and their families
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- Dr. Xiaozhong Wen
- Divya Coudhary
- Dr. Claire Cameron
- Dr. Todd Rideout

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BEFORE I BEGIN: THANK YOU

To the people of the South Ward, Newark, NJ, who have dedicated their time, perspective, and effort to the work described in this presentation.

To my co-authors & research team members from South Ward Promise Neighborhood, FARE, Center for Food Allergy & Asthma Research (CFAAR) & Northwestern University:

Jenna Yost, Christopher M. Warren, PhD, Ruchi Gupta, MD, MPH, Marie Malloy, Ososese Enaholo, MPH, Isabel K. Galic, & Justine Asante
Racial Differences in Food Allergy Phenotype and Health Care Utilization among US Children

- Multi-center, retrospective cohort study of children aged 0-17 years with FA seen in allergy/immunology clinics at 2 US urban tertiary care centers
- N=817
- 35% Black, 12% Hispanic, 53% non-Hispanic white

Average duration of FA specialist follow-up care:
- White: 3.2 years (SD=2.1)
- Black: 2.3 years (SD=2.4)
- Hispanic: 2.2 years (SD=2.3)

National data report that although overall rates of fatal food-related anaphylaxis did not increase significantly from 1999-2010, rates increased more than three-fold among AA males.

AA girls are at a nearly two-fold greater risk of food-related fatal anaphylaxis than White girls.

AA boys are at a three-fold greater risk relative to their White counterparts.

FARE VISION

**PATIENT-CENTERED RESEARCH**
To understand barriers to and promotors of access to quality care, safe foods and clinical trial participation.

**PROGRAMS**
Community engagement, education, & outreach programs to holistically address SDOH factors,

**PARTNERS & POLICY**
Leverage existing and new local, state, and federal partners & collaborators to expedite collective impact, build trust, & institutionalize change.

**VISION:** A world where all those impacted by food allergies, regardless of race, socio-economic status or geography, have access to quality food allergy care, safe foods and are equitably represented in food allergy research.

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Community-Based Participatory Research (CBPR)

**CBPR:**
- “A collaborative process that equitably involves all partners in the research process and recognizes the unique strengths that each brings.”
- Driven by empowered community partners that have an equal seat at decision making table to drive change (i.e., policy).

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OUR CBPR PROJECT: 
FARE COMMUNITY ACCESS INITIATIVE (CAI)

CBPR program underway in the South Ward of Newark, NJ

**Newark/ South Ward Statistics**

**Access to Primary Care** – A Beth Israel report concluded that there was a need for 36 additional PCPs in the SW and that both children and adults utilized the ED at higher rates statewide (SWPN, 2016)

**Asthma** – An estimated 25 percent of Newark children have asthma (ACNJ, 2016) and ED usage for asthma was higher than the rates statewide (NYU & SWPN, 2016)

**Food Allergy**—22% of SW household may have FARE (Child Trends & SWPN, 2021)

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**CAI PHASE I: COMMUNITY NEEDS ASSESSMENT**

Responses collected from 724 residents of Newark’s South Ward

- Survey distributed July 2021
- Catchment area: ZIP Codes: 07108, 07112, 07114
- Survey responses were obtained electronically via email and mobile in REDCap

<table>
<thead>
<tr>
<th>% of Respondents</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invitation from my church</td>
<td>24</td>
</tr>
<tr>
<td>Invitation via email/social media from another organization or person</td>
<td>69.3</td>
</tr>
<tr>
<td>Email invitation from FARE</td>
<td></td>
</tr>
<tr>
<td>Invitation via email or social media from SWPN</td>
<td></td>
</tr>
</tbody>
</table>
Community Needs Assessment Demographics

61% Non-white respondents
~85% had a household income below the US median

Gender
- Non-binary: 1%
- Male: 49%
- Female: 50.8%

Race/Ethnicity
- American Indian: 9.4%
- Asian: 4.1%
- Black: 28.9%
- Hispanic: 15.9%
- Middle Eastern/North African: 1%
- Pacific Islander: 1.9%
- White: 38.9%

Prevalence of Specific Food Allergies

Burden of shellfish, finned fish allergy greater in the South Ward. What are the potential cultural implications?
Newly Diagnosed Resources Needed

Around 60% of respondents did not receive or did not find helpful standard FA resources like ECPs, HCP referrals, and educational/instructional information.

87% ALLERGIST-DIAGNOSED FA, YET EAI BARRIERS & MISCONCEPTIONS EXIST

Has the food-allergic person ever been prescribed an epinephrine auto-injector (EAI)?

I have never heard of epinephrine
I don't know
No, they have never been prescribed epinephrine
Yes, they received, but the prescription is not filled
Yes, they currently have epinephrine, but it is expired
Yes, they currently have epinephrine

Reasons for not filling EAI prescription (among those who were prescribed but didn’t fill)

- The food-allergic person has never had a reaction
- The food allergic person's allergy is not severe
- They're too bulky/inconvenient to carry
- Cost
- Didn't think the food allergic person needed it
- Already had one or more EAs
GREAT DISPARITY IN NEWARK EAI ACCESS COMPARED WITH US POPULATION ACCESS

In the past week, how often was an epinephrine auto-injector available to the food-allergic person if needed (accessible in 5 min)?

Never
Rarely
Some of the time
Most of the time
All of the time

% of Respondents

US
CAI Newark

NEWARK: Precautionary allergen labeling (PAL) such as “may contain milk” or “this product is produced on equipment shared with tree nut products” is required by law.

TRUE
FALSE
I don’t know

69.4
26.5
4.1

NEWARK: Precautionary allergen labeling (PAL) such as “may contain milk” or “this product is produced on equipment shared with tree nut products” is required by law.

Compared with 55% of FARE constituents, only 26% of FA Newark respondents correctly answered

Northwestern University/Center for Food Allergy & Asthma Research/FARE PAL Study

<table>
<thead>
<tr>
<th>N</th>
<th>% of Total Correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>1675</td>
<td>55.7 (False)</td>
</tr>
</tbody>
</table>

PERCEPTION OF FA FATAL REACTION PROBABILITY GREAT IN NEWARK VS US POP

More South Ward FA residents think there is some chance of death with accidental exposure compared to US population... perhaps contributing to greater emotional burden.

FA PARENTS NEED MORE SUPPORT

“It shouldn’t have taken my child to have an allergic reaction for [family members] to understand how serious food allergy is.” – Community Participant

Please indicate if YOUR CHILD with food allergies has ever reported experiencing the following due to their FA:

- Being bullied: 5.2%
- Fear of eating: 19.5%
- Loneliness: 19.2%
- Anger: 19.9%
- Anxiety: 25%

Please indicate if YOU have ever reported experiencing the following due to child’s FA:

- Feeling helpless: 8.6%
- Feeling overwhelmed: 11.7%
- Feelings of depression: 10.4%
- Being bullied: 11.9%
- Loneliness: 16.9%
- Anger: 16.4%
- Anxiety: 18.9%
About a 1/4 face barriers to food access due to cost or availability

I have difficulty obtaining allergy safe food ... due to the cost of the food

- Strongly agree
- Agree
- Neither agree nor disagree
- Disagree
- Strongly disagree

... due to the lack of availability of allergy-safe food in my community

- Strongly agree
- Agree
- Neither agree nor disagree
- Disagree
- Strongly disagree

“*It is difficult to find allergy-free foods in grocery stores. There are no designated allergy-friendly sections in supermarkets. This makes it difficult for people to know what they can and cannot eat*” – Community Participant

“When I moved out here I [realized] it’s a food desert. Where are the supermarkets? What about people who don’t have a car... who take the bus or a train? It’s harder to [to access] healthier options” – Community Participant
Within the past 12 months, how often were you worried that your food would run out before you got money to buy more?

- Often
- Sometimes
- Never
- I don't know

Within the past 12 months, how often did the food you bought not last and you didn’t have money to get more?

- Often
- Sometimes
- Never
- I don't know

About 72% worried at least sometimes that they wouldn’t have enough money for food and did indeed run out of food.

70% utilized food banks; often facing limited substitution options due to FA.

NEXT STEPS: IMPACT SOCIETAL FACTORS TO IMPROVE FA OUTCOMES

- **CAI Newark Phase II**
  - Launch patient education & support efforts – led by the community, for the community – for newly diagnosed & beyond
  - Expand multistakeholder partnerships to improve reach and buy in
  - Support policy that improve access to food (i.e., USDA/HHS)
  - Expand FA training for various stakeholders (i.e., WIC staff, PCPs, mental health specialists)
  - Expand CAI to other cities and link to FARE Clinical Network sites, FARE Data Commons for improved access to care

Holistic programs to improve FA health outcomes equitably

Social Engagement

Healthcare Infrastructure

Food Security

Economic Opportunity

Education Opportunity
Racial disparities in food allergy exist.

Community-Based Participatory Research efforts like Community Access Initiative can help to identify and address these disparities. It requires:

- Inclusive Data
- Multistakeholder Partners
- Holistic Programs

THANK YOU!

Anita Roach
aroach@foodallergy.org
Food Allergies and Management

- Estimated that around 8% of children, 11% of adults have FAs in the U.S.
  Gupta et al., Pediatrics. 2018; Gupta et al., JAMA Netw Open. 2019

- There is no current cure
  - Avoidance diets
  - Epinephrine usage

THE EIGHT FOOD ALLERGEN
HEAVY HITTERS

1. MILK
2. EGGS
3. FISH
4. SHELLFISH
5. TREE NUTS
6. PEANUTS
7. WHEAT
8. SOYBEANS
Allergy Treatments

Experimental trials:
- Sublingual Immunotherapy (SLIT)
- Epicutaneous Immunotherapy (EPIT)
- Drug + OIT adjunct treatments

- **Oral Immunotherapy**: an emerging method of therapy that involves the gradual introduction of offending food allergens to sensitized individuals
- FDA-approved for Peanut allergy intervention

POISED (NCT02103270)

Peanut Oral Immunotherapy: Safety, Efficacy, and Discovery

OIT and $\gamma\delta$ T cells

$\gamma\delta$ T cells are a major T cell subset of intraepithelial lymphocytes (IELs)

- Regulation of immunosuppressive functions of IELs
- Help develop tolerance to allergens

What are $\gamma\delta$ T cells?

- They make up a small subset of T cells
  - Characterized by their T-cell receptors (TCRs) composing of $\gamma$ and $\delta$ chains
- T cells are lymphocytes with specific antigen receptors
  - Specificity for particular a epitope
- Typically found in epithelial and mucosal tissue
- First lines of defense against pathogens
- Can recognize antigens without MHC molecules
Why study $\gamma\delta$ T cells in the context of OIT?

- How are $\gamma\delta$ T cells affected after undergoing OIT?
- GI side effects are most common with OIT
  - Abdominal pain, vomiting, cramping, EoE, oral itching, etc.
- To reveal transcripts and pathway signatures relevant to peanut desensitization mechanisms during OIT

Hypothesis

If a participant is undergoing oral immunotherapy, then we may observe differences in the composition of $\gamma\delta$ T cells between pre-OIT and post-OIT phases.

FA patients may have an increase of $\gamma\delta$ T cells in their GI tract.
**Mechanistic Workflow: Post-Biopsy Collection**

What were samples used for?

**Methods | Immunofluorescence Staining**

Immunostaining Workflow
Identification of \( \gamma \delta \) T cells Through Confocal

Representative immunofluorescent staining of duodenal biopsy section for one participant showing CD3, T cell receptor delta and merged CD3/TCR\( \delta \)

Increase in the Number of \( \gamma \delta \) T cells at week 104 of OIT

Number of \( \gamma \delta \) T cells in 6 active (peanut OIT-treated) participants pre- and post-OIT

Total number of CD3 and TCR delta double positive cells
RNAseq cell sorting

Volcano plots depicting differentially expressed (DE) transcripts

(a) Wk52 Vs Wk0
(b) Wk104 Vs Wk0
(c) W104 Vs Wk52
**RNAseq Heat Map**

Heatmap depicting DE transcripts across the three time points

![Heatmap Image](image)

**RNAseq Findings**

Immune-related Pathways featured in KEGG pathway analysis accounting for DE genes

- hsa04330 Notch signaling pathway
- hsa04664 Fc epsilon RI signaling pathway
- hsa04062 Chemokine signaling pathway
- **hsa04660 T cell receptor signaling pathway**
- hsa00830 Retinol metabolism
- hsa04350 TGF-beta signaling pathway
Summary

- A trend of increase in the number of $\gamma\delta$ T cells in the examined duodenal biopsies post-OIT is observed.
- Differentially expressed genes among $\gamma\delta$ T cells imply immune regulation post-OIT.
- Peanut OIT induced frequency and transcriptional alterations in GI-resident $\gamma\delta$ T cell population.
- We should continue to investigate the their role in OIT and tolerance to food allergens.

Multiple Choice Questions

1. Which cytokine will be predominantly expressed by $\gamma\delta$ T cells under homeostatic conditions?
   a. IFN-\(\gamma\)
   b. IL17
   c. TGF-\(\beta\)
   d. TNF-\(\alpha\)
Multiple Choice Questions

1. Which cytokine will be predominantly expressed by γδ T cells under homeostatic conditions? 
   a. IFN-γ  
   b. IL17  
   c. TGF-β  
   d. TNF-α

Multiple Choice Questions

1. Which antibody subtype causes pathogenesis of food allergy? 
   a. IgE  
   b. IgA  
   c. IgG  
   d. IgD
Multiple Choice Questions

1. Which antibody subtype causes pathogenesis of food allergy?
   a. IgE
   b. IgA
   c. IgG
   d. IgD

Acknowledgements

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Screening Children with IgE-Mediated Food Allergy for Eosinophilic Esophagitis

Peter Capucilli, MD
Allison Ramsey, MD
Linh-An Tuong, MD
S. Shahzad Mustafa, MD
Rochester Regional Health

Historical background

- Rare case reports of EoE in the 1960-70s. Initially unclear if part of spectrum of eosinophilic gastroenteritis.
- Increase number of case descriptions in 1990s and appreciation of EoE as a distinct entity in 1993 (Attwood and colleagues).

- Link between Food Allergy (FA) and EoE – 1995
  - Kelly and Sampson
    - 10 patients (age 8mo-12yrs)
    - Treated with >6wks amino-acid formula
    - Pre-post endoscopy
  - Dobbins (1977) – 51 year old with GERD, FA and esophageal eosinophilia

Historical background

- 2007: First consensus guidelines published (TIGERS)
  - Key concepts solidified
    - Summation of clinical symptoms
    - >15 eos per HPF
    - Absence of GERD
  - Number of publications related to EoE ↑↑↑

- 2011: Guidelines updated by TIGERS group
  - Emphasis on distinguishing “EoE” from “esophageal eosinophilia”
  - Differentiation of “PPI responsive” esophageal eosinophilia

- 2018 Updated International Consensus – AGREE Conference
  - Removal of PPI trial to assess responsive esophageal eosinophilia
## Diagnostic delay

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Median (IQR) Age (years) Diagnosis</th>
<th>Median (IQR) Age (years) Symptom Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11</td>
<td>3.0 (1.9-6.0)</td>
<td>1.1 (0.4-3.0)</td>
</tr>
<tr>
<td>11-17</td>
<td>12.0 (9.0-13.0)</td>
<td>10.0 (4.0-12.0)</td>
</tr>
<tr>
<td>Adults</td>
<td>29.0 (18.0-39.0)</td>
<td>19.0 (12.0-30.0)</td>
</tr>
</tbody>
</table>

Chehade et al, 2018
Schoepfer et al, 2013
Diagnostic delay

- Delay between symptom onset and EoE diagnosis
  Median [IQR] years: 1.5 [0.7-4.0]
- Delay associated with hx of IgE-FA and AD
- Significant association between delay of onset and strictures formation


Association of Atopy and EoE

- Allergic Rhinitis (57-70%)
- Asthma (27-60%)
- Atopic Dermatitis (6-48%)
- IgE-Food Allergy (24-68%)

Capucilli and Hill, Clin Rev Allerg Immunol, 2019
Association of Atopy and EoE

<table>
<thead>
<tr>
<th>Reference</th>
<th># of Pts</th>
<th>Age (Yrs)</th>
<th>Asthma</th>
<th>Allergic Rhinitis</th>
<th>Atopic DERM.</th>
<th>Food Allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population</td>
<td></td>
<td></td>
<td>10%</td>
<td>20-40%</td>
<td>5-20%</td>
<td>1-6%</td>
</tr>
<tr>
<td>Spergel</td>
<td>620</td>
<td>8m-20</td>
<td>50%</td>
<td>61%</td>
<td>21%</td>
<td>16%</td>
</tr>
<tr>
<td>Assad</td>
<td>89</td>
<td>3m-18 yr</td>
<td>39%</td>
<td>30%</td>
<td>19%</td>
<td>9%</td>
</tr>
<tr>
<td>Suggnanam</td>
<td>45</td>
<td>3m-16 yr</td>
<td>66%</td>
<td>93%</td>
<td>55%</td>
<td>24%</td>
</tr>
<tr>
<td>Guajardo</td>
<td>39</td>
<td>1m-31</td>
<td>38%</td>
<td>64%</td>
<td>26%</td>
<td>23%</td>
</tr>
<tr>
<td>Roy-Ghanata</td>
<td>23</td>
<td>18-57</td>
<td>26%</td>
<td>78%</td>
<td>4%</td>
<td>--</td>
</tr>
</tbody>
</table>

Ruffner, MD Annual Practical Review for the Clinician, 2018

EoE following IgE-FA

- 17 children outgrew IgE-FA developed EoE to same food
- 67 subjects with ourgrew IgE-FA and developed EoE to different food

EoE and The Atopic March

Can we screen children with IgE-FA for EoE?
Practical questions

- Do you have trouble swallowing foods?
- Do you have heartburn? Reflux?
- Do you have nausea or vomiting with eating?
- Do you regurgitate food?
- Does the food get stuck when you eat?
- Does it take longer than others to eat?
- Do you need to cut your food into small pieces?
- Do you need to use liquids to help swallow food?
- Do you have more trouble swallowing meats? Breads? Rolls etc.
- Do you have chest pain when you eat?
- Does it take a long time for food to get down once swallowed?
- Do you avoid eating in front of other people?
- Have people around you noticed a problem?

Dysphagia

- Correlated most strongly with histopathology/eosinophil activity, especially proximal esophagus, p≤0.0049
- Most strongly correlated with esophageal gene transcription
Objectives

• Determine utility and feasibility of screening children with IgE-mediated food allergy (IgE-FA) for symptoms of Eosinophilic Esophagitis (EoE)

Methods

• Pilot study
• 3 outpatient clinic sites within hospital based practice
• April 2021-September 2021 (study ongoing)
• Administered Pediatric Eosinophilic Esophagitis Symptom Severity Module (PEESS):
• Additional Questions: “Do you ever feel food going down after swallowing?”
Pediatric Eosinophilic Esophagitis Symptom Severity Module (PEESS)

- 20 question survey measuring Frequency and Severity of symptoms
  - Parent - 2-18 years
  - Pediatric patients – 8-18 years
- Graded on 0-4 scale
  - Frequency: Never-Almost always
  - Severity: Not bad at all-Very bad
- 6 Questions related to Dysphagia
- 14 questions related to other EoE-relevant symptoms:
  - Odynophagia
  - Heartburn
  - stomach pain
  - Nausea/Vomiting
  - Regurgitation
  - Satiety
Outcomes

• Primary Outcomes
  • Positive response on any of the 6 questions related to dysphagia with a score of ≥2.
    • Symptoms frequency at least 1 or more times per week, daily or 2 or more times a day, OR
    • Severity of symptoms rated “Kind of bad,” “Bad,” or “Very Bad.”

• Secondary Outcomes
  • Positive response to remaining survey items

Results

• Initial 5 months of study
  • 181 completed surveys (69% with child survey complete)
  • 171 patients with IgE-food allergy diagnosed only
  • 10 patients with IgE-food allergy and EoE diagnosed

• Demographics
  • Mean age (range): 9 (2-18) years
  • 65% male, 35% female
  • 50% with Allergic rhinitis
  • 30% with Asthma
  • 22% with Atopic dermatitis
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pediatric Survey</th>
<th>Parent survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive to dysphagia question</td>
<td>19 (15%)</td>
<td>15 (10%)</td>
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</tbody>
</table>
## Results

<table>
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<th>Parent survey</th>
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<tr>
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</tr>
<tr>
<td>Positive to Additional question</td>
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<td>N/A</td>
</tr>
<tr>
<td>Positive to Additional question ONLY</td>
<td>20 (16%)</td>
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<tr>
<td>Positive to Additional question</td>
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</tr>
<tr>
<td>Positive to Additional question ONLY</td>
<td>20 (16%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Total positive response</td>
<td>39 (30%)</td>
<td>15 (10%)</td>
</tr>
</tbody>
</table>

• 14 of 15 (93%) children with positive dysphagia questions responses reported positively to at least 1 or more additional survey question in different symptom category.

• Of the 20 patients with positive additional question response, 64% responded positively to at least 1 or more additional survey questions in a different symptom category.

• Of the 10 children with established EoE, only 4 reported dysphagia symptoms.
Results

• Concordance between parent and child response was low.
  • Only 6 patients/parents showed concordance for positive dysphagia responses.
  • A negative parent response was elicited in 63% of cases in which child reported positive dysphagia symptoms.

Limitations

• Initial phase pilot study – unclear if positive responses correlate directly with EoE findings on endoscopy
• Recall bias
• Unclear significance of supplemental question
• Lack of control group
Next Steps

• Large scale screening of kids with food allergy?
• Who needs scope?
• Other methods of screening?
• Significance of dysphagia?

Take Away

• A high proportion of children and parents with IgE-FA endorse symptoms of dysphagia raising concern for EoE.
• Feeling of food passing following swallowing was also endorsed by a large number of patients who also report other symptoms associated with EoE and may be an important symptom to identify esophageal pathology.
• Symptoms may go unnoticed by parents and physicians in the absence of formal screening.
Screening Children with IgE-Mediated Food Allergy for Eosinophilic Esophagitis

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Rochester Regional Health
Atopic dermatitis mediates the association between an IL4Rα variant and food allergy in school-aged children

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Division of Allergy and Immunology
Boston Children’s Hospital
Harvard Medical School
Boston, Massachusetts

Wanda Phipatanakul, MD, MS
PI: SICAS

Background

- Food allergy and atopic dermatitis often coexist in infancy and early childhood as part of the atopic march, and both are associated with genetic variations

- The dual-allergen exposure hypothesis proposes that allergic sensitization to food can occur through the skin, whereas early consumption of food protein induces oral tolerance
Objective

We describe an association of food allergy diagnosis and a human interleukin 4 receptor alpha chain gene (IL4Ra) variant mediated through atopic dermatitis in inner-city children, which is also associated with severity of food allergy reaction.

Predicted asthma symptom days per 2-week period associated with classroom endotoxin levels stratified by IL4Ra-Q576R genotype demonstrate a gene by environment (G x E) interaction.

Methods

• 433 elementary school-age children with asthma enrolled in the School Inner-City Asthma Study underwent genotyping for a IL4Rα-Q576R polymorphism

• Surveys were administered to determine physician-diagnosed FA and associated allergic responses

• Genotypes modeled as a 3-group categorical variable (Q/Q, Q/R, or R/R genotypes, with the Q/Q genotype as the reference group)

To test the hypothesis AD mediates the association between genotype and FA, we performed two adjusted logistic regression models:

1) AD predicted from genotype and

2) FA predicted from AD and genotype

We evaluated the association between genotype and severe FA reactions (defined as trouble breathing) using multivariate models.
Demographics

<table>
<thead>
<tr>
<th>N (%) or mean (SD)</th>
<th>All (n=433)</th>
<th>QQ (n=119)</th>
<th>QR (n=186)</th>
<th>RR (n=128)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>8.0 (1.9)</td>
<td>8.3 (1.9)</td>
<td>7.9 (2.0)</td>
<td>7.9 (1.8)</td>
<td>0.19</td>
</tr>
<tr>
<td>Female</td>
<td>203 (47)</td>
<td>58 (49)</td>
<td>81 (44)</td>
<td>64 (50)</td>
<td>0.47</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>31 (7)</td>
<td>18 (15)</td>
<td>10 (5)</td>
<td>3 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black</td>
<td>130 (30)</td>
<td>15 (13)</td>
<td>55 (30)</td>
<td>60 (47)</td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>192 (44)</td>
<td>68 (57)</td>
<td>87 (47)</td>
<td>37 (29)</td>
<td></td>
</tr>
<tr>
<td>Other/mixed</td>
<td>80 (18)</td>
<td>18 (15)</td>
<td>34 (18)</td>
<td>28 (22)</td>
<td></td>
</tr>
<tr>
<td>Income &lt;$25K</td>
<td>145 (44)</td>
<td>33 (35)</td>
<td>59 (43)</td>
<td>53 (52)</td>
<td>0.05</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>193 (45)</td>
<td>41 (35)</td>
<td>86 (47)</td>
<td>66 (52)</td>
<td>0.02</td>
</tr>
<tr>
<td>Food allergy</td>
<td>82 (19)</td>
<td>22 (18)</td>
<td>33 (18)</td>
<td>27 (21)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

The role of the IL4Rα variant in atopic dermatitis and food allergy

Indirect effect of QR on food allergy: OR=1.18 [0.99,1.39], P=0.06
Indirect effect of RR on food allergy: OR=1.26 [1.04,1.52], P=0.02
### Severe food allergy symptoms by genotype

<table>
<thead>
<tr>
<th>Symptom</th>
<th>QQ (n=22)</th>
<th>QR (n=33)</th>
<th>RR (n=27)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Throat tightness</td>
<td>7 (32)</td>
<td>9 (27)</td>
<td>13 (48)(^a)</td>
<td>0.047</td>
</tr>
<tr>
<td>Coughing</td>
<td>7 (32)</td>
<td>9 (27)</td>
<td>6 (22)</td>
<td>0.90</td>
</tr>
<tr>
<td>Wheezing</td>
<td>5 (23)</td>
<td>11 (33)</td>
<td>9 (33)</td>
<td>0.42</td>
</tr>
<tr>
<td>Trouble breathing</td>
<td>5 (23)</td>
<td>12 (36)(^a)</td>
<td>13 (48)(^a)</td>
<td>0.04</td>
</tr>
<tr>
<td>Drop of blood pressure</td>
<td>2 (9)</td>
<td>1 (3)</td>
<td>1 (4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Passing out</td>
<td>2 (9)</td>
<td>0 (0)</td>
<td>3 (11)</td>
<td>0.64</td>
</tr>
<tr>
<td>Itchy throat/mouth</td>
<td>10 (45)</td>
<td>18 (55)</td>
<td>17 (63)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Observed N (%). P-values adjusted for age, gender, and race/ethnicity.
\(^a\): p<0.05 vs QQ

### Food allergies by genotype

<table>
<thead>
<tr>
<th>Food</th>
<th>QQ (n=119)</th>
<th>QR (n=186)</th>
<th>RR (n=128)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>8 (7)</td>
<td>19 (10)</td>
<td>12 (9)</td>
<td>0.62</td>
</tr>
<tr>
<td>Fish</td>
<td>3 (3)</td>
<td>2 (1)</td>
<td>3 (2)</td>
<td>0.55</td>
</tr>
<tr>
<td>Fruits</td>
<td>5 (4)</td>
<td>9 (5)</td>
<td>9 (7)</td>
<td>0.83</td>
</tr>
<tr>
<td>Grains</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>0.73</td>
</tr>
<tr>
<td>Soy</td>
<td>2 (2)</td>
<td>2 (1)</td>
<td>7 (5)(^*)</td>
<td>0.10</td>
</tr>
<tr>
<td>Egg</td>
<td>2 (2)</td>
<td>4 (2)</td>
<td>9 (7)(^*)</td>
<td>0.10</td>
</tr>
<tr>
<td>Nuts from trees</td>
<td>7 (6)</td>
<td>9 (5)</td>
<td>7 (5)</td>
<td>0.90</td>
</tr>
<tr>
<td>Shellfish</td>
<td>5 (4)</td>
<td>7 (4)</td>
<td>7 (5)</td>
<td>0.77</td>
</tr>
<tr>
<td>Vegetables</td>
<td>5 (4)</td>
<td>0 (0)(^*)</td>
<td>2 (2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Seeds</td>
<td>3 (3)</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Milk</td>
<td>5 (4)</td>
<td>8 (4)</td>
<td>3 (2)</td>
<td>0.57</td>
</tr>
<tr>
<td>Meats</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Observed N (%). P-values adjusted for age, gender, and race/ethnicity.
\(^*\): p<0.01 vs QQ
\(^a\): p<0.03 RR vs QR/QQ
Trouble breathing

![Bar graph showing observed and adjusted percentages for QQ (n=22), QR (n=33), and RR (n=27). P=0.046 vs QQ for QQ, P=0.01 vs QQ for QR, and P=0.01 vs QQ for RR.]

Individual food allergies

![Bar graph showing percentages of individual food allergies (Eggs and Soy) for QQ, QR, and RR. P=0.01 (vs. QR+QQ) for Eggs and Soy.]

Trouble breathing

Individual food allergies
Summary

1. AD mediates association between food allergy and IL4Rα variant
2. Increased risk of food allergy severity (trouble breathing) in asthma cohort with risk allele
3. Increased risk of individual food allergies (egg, soy) with risk allele
4. These findings lend support to the hypothesis food allergy develops through epicutaneous exposure to food allergens
5. Findings relevant to ensure appropriate prevention of epicutaneous food exposure prior to oral exposure to decrease risk of sensitization to food proteins and development of IgE-mediated food allergy

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- R01 AI 065617
- K23 AI 143962
- T32 AI 007512