Updates on Pediatric Asthma

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Risk of COVID-19 in Peds Asthma

• 6,515 children with asthma matched to non asthmatic controls (n=13,030)
• Age – median 11 years (range 8-14 years)

  • Dx of asthma was a/w:
    – Higher likelihood of being tested (10.4% vs 6.8%, p< 0.001)
    – Decreased risk of SARS-CoV-2 infection (RR: 0.67, 95% CI: 0.49-0.92).
    • Stronger in kids on ICS (RR: 0.60, 95% CI: 0.38-0.94) or with atopy (RR: 0.59, 95% CI: 0.39-0.88)
    • 66 children with asthma developed SARS-CoV-2 infection, none hospitalized

Impact of COVID-19 on Peds Asthma

PeARL Multi-national Cohort

- 1,054 children with asthma
- 505 non-asthmatic controls
- ages 4-18 years
- 25 pediatric departments from 15 countries


Delta variant

Increasing COVID-19 hospitalizations among U.S. children and adolescents since the rise of the Delta variant

Hospitalizations among ages 0-4

Hospitalizations among unvaccinated adolescents

10x increase

10x higher than fully vaccinated

PREVENT COVID-19 AMONG CHILDREN

Everyone ages 2 and up:
Wear a mask in public indoor spaces, schools, and childcare centers

Everyone ages 12 and up:
Get vaccinated

www.cdc.gov/mmwr/volumes/70/wr/mm7036e2.htm
To Step Down or Not to Step Down...

Pros:
• Reduction in child’s steroid exposure
• Reduction in medication costs

Cons:
• Misinterpretation of control
• Risk of exacerbations
• ED visits potentially exposing patient to COVID and contributing to constraints in resources
• Potential benefit of ICS on reduction of inflammation and viral replication


Updated 2020 NIH Asthma Guidelines

• Intermittent ICS+SABA at onset of RTI for 0-4 years
• SMART for 4+ years old
• Daily ICS vs PRN ICS-LABA for 12+ years old
• FeNO
• Allergen Mitigation
• SCIT and SLIT for asthma
Intermittent ICS+SABA at onset of RTI for 0-4 years

*** Recommends against temporary doubling/quadrupling ICS for adherent patients on daily ICS already (may be a consideration for non-adherent patients)

SMART FOR 4+

Can use daily ICS-formoterol as well as PRN as rescue
- Ages 4-11 – do not exceed 8 puffs in 24 hours
- Age 12+ - do not exceed 12 puffs in 24 hours
PRN ICS+SABA, addition of LAMA

- 12+ years old
- For mild persistent asthma can use daily ICS + PRN SABA or concomitant PRN ICS + SABA
- For uncontrolled persistent asthma, recommended to add LABA to ICS. If LABA not used, can add LAMA
- Add LAMA to ICS-LABA if still uncontrolled

Additional Updates

- FeNO recommended for 5+ as an adjunct to diagnose and management
  - Should not be used alone
  - Do not use in kids 0-4 years with recurrent wheezing to predict asthma
- Allergen mitigation should be used in those sensitized and symptomatic, but not in those who have negative testing/asymptomatic
- SCIT recommended as adjunct therapy in kids 5+ with mild to moderate asthma
- SLIT not recommended for asthma management alone
  - Consider benefits for allergic rhinitis/conjunctivitis
SCIT in < 4 years old

- Children in Bronx NY with recurrent wheezing or physician diagnosed asthma ages 18-47 months received 3 years of multi-allergen SCIT vs control
- N=50 children (27 SCIT, 23 placebo), median age 3 years
- 20/27 completed at least 2 years
- 1 in 3 to 1 in 4 injection visits missed overall
- No difference in asthma medication and symptoms score
- Marginal improvement in nasal symptom scores in SCIT group in per protocol analysis
- SCIT group used slightly more medication
- Improved QoL in SCIT group compared with controls
  - SCIT group started with lower QoL scores at baseline


Allergen Mitigation at School

- 236 students with asthma in 41 urban elementary schools in the Northeastern US randomized to school wide integrated pest management (IPM) vs HEPA filter purifiers in classrooms
- 98% of classrooms had detectable mouse allergen levels
- Mean symptom days
  - 1.5 (IPM) vs 1.9 (no IPM)
  - 1.6 (HEPA) vs 1.8 (sham HEPA)
  - Neither statistically significant

Recurrent Wheezing Phenotypes

- ≤ 6 years old with poor control of recurrent wheezing despite treatment for ≥ 4 months underwent BAL


Gestational vitamin D

Maternal Stress and Depression

Key Points

- Asthma does not seem to be a major risk factor for severe COVID-19 infection
- Consider previous h/o exacerbations, time of year when stepping down on asthma therapy
- Review the new guidelines: 0-4 ICS + SABA at onset of respiratory infection, SMART, FeNO can be a helpful additional diagnostic tool, SCIT is still a good option for persistent asthma management in sensitized/symptomatic kids
- BAL may be a helpful tool to determine underlying causes for wheezing
- Maternal stress, depression and vitamin D may be linked to childhood asthma

Thank you ACAAI, AAP and Dr. Todd Mahr!
Food Allergy
Non-treatment

THERESA A. BINGEMANN, MD
ASSOCIATE PROFESSOR OF PEDIATRICS AND MEDICINE
UNIVERSITY OF ROCHESTER

Disclosures

Consultant – ALK regarding allergen immunotherapy
LEAP study and current recommendations

<table>
<thead>
<tr>
<th>Infant risk group</th>
<th>Recommendation</th>
<th>Earliest age of peanut introduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe eczema, egg allergy or both</td>
<td>Strongly consider evaluation by the measurement and/or SPT and, if necessary, an OFC. Based on test results, introduce peanut-containing foods.</td>
<td>4-6 months</td>
</tr>
<tr>
<td>Mild to moderate eczema</td>
<td>Introduce peanut-containing foods</td>
<td>Around 6 months</td>
</tr>
<tr>
<td>No eczema or any food allergy</td>
<td>Introduce peanut-containing foods</td>
<td>Age appropriate and in accordance with family preferences and cultural practices</td>
</tr>
</tbody>
</table>

86.1% relative reduction


JACI 2017;139:29-44
FRATRIES study

The Finding the Risk of Anaphylaxis and Testing Rationale in younger Siblings

Prospective cohort study (n=154)

Designed to assess the risk of peanut introduction without risk stratification in siblings of peanut allergic children

Double-blind testing and parent led introduction

5.2% of the population had IgE mediated symptoms upon introduction

Peanut consumption habits and incidence of new peanut allergy in a cohort of younger siblings of peanut allergic children

![Graph showing peanut consumption habits and incidence of new peanut allergy](image)

* * * p = 0.064
* p = 0.054
* p = 0.17

**FIGURE 1.** Observed risk of developing allergy to peanut based on consumption habits. P values were determined by Fisher exact test.
Age and eczema severity, but not family history, are major risk factors for peanut allergy in infancy

Rates of peanut allergy

Population:
- 321 infants 4-11 months of age with:
  - no history of peanut exposure or allergy testing
  - at least one risk factor

Procedures:
- Skin prick test and oral food challenge (or observed feeding) to determine peanut allergy status

Risk Modification:
- Higher age and SCORAD (SCORing Atopic Dermatitis) score increase risk
- In the absence of eczema, family history confers very little risk
- Among those with eczema, food allergy other than peanut increases risk

FIG 1. Percent peanut allergic by risk category. Eczema: Moderate-severe eczema by inclusion criteria; no eczema, includes those with eczema who did not meet the inclusion criteria; FA, history of a nonpeanut food allergy diagnosed by a physician; FH, family history, defined as a first-degree relative with peanut allergy; N, total number in each group.

FIG 2. Probability of peanut allergy by age and objective SCORAD score. Smoothed LOWESS curve, bandwidth 0.8.
Unintended consequences (of early introduction)

What should not be introduced?

Whole nuts
Thick clumps of peanut butter
Features of FPIES in adults

Clinical history:
- 2 or more episodes of GI symptoms
- Specific food trigger
- Within 1-12 hours
- No symptoms of IgE-mediated reaction
- Resolution with food elimination
- No other explanation for symptoms

Median age of onset 37 years (IQR 5.5)
- 71% female

Seafood 66.7%
- Mollusks 58.3%
- Crustaceans 29.2%
- Fish 29.2%
THANK YOU!

Theresa_Bingemann@URMC.Rochester.edu
7 for 11 Food Allergy Therapies

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Associate Professor of Pediatrics & Internal Medicine
Director, Food Allergy Center at Children’s Health
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Rewards

Continuous and Daily Oral Immunotherapy for Peanut Allergy: Results from a 2-Year Open-Label Follow-On Study

- After 300 mg daily peanut OIT for at least 24 weeks then divided into various dosing regimen for 28-56 weeks: Daily (1.5 – 2 years) OR every other day (4 – 24 weeks) → twice weekly (24-56 weeks)
- Daily dosing group retained highest desensitization rate
- Staggered dosing had highest discontinuation rate, higher rate of TEAEs and higher rate of systemic allergic reactions

TAKE HOME POINTS:
- Daily dosing of peanut OIT for at least two years is likely more beneficial than a staggered dosing approach
- Long-term flup is necessary to understand if staggered dosing might be appropriate after a longer maintenance period
Oral Immunotherapy (egg)

A Randomized, Open-Label Trial of Hen’s Egg Oral Immunotherapy: Efficacy and Humoral Immune Responses in 50 Children

- High baseline egg white IgE and polysensitization to Gal d1-4 related with OIT discontinuation and failure to achieve the maintenance dose at 8 mos
- Most patients with high baseline egg white IgE and polysensitization were able to achieve desensitization though it took longer.

TAKE HOME POINTS:
- OIT appears to accelerate development of desensitization in patients who may develop natural tolerance with time (possibly remission/SU development though not measured in this report)
- For those who are unlikely to outgrow, most may be desensitized with a prolonged schedule
- Maintaining protective benefit is likely to require continuous exposure to allergen

Oral Immunotherapy (wheat)

Low-dose-oral immunotherapy for children with wheat-induced anaphylaxis

- 5-18 y/o children (n=16) with h/o wheat anaphylaxis and positive OFC to 53 mg wheat protein
- Hospital admission for 5-day build-up to maximum 53 mg with maintenance of 53 mg/d x 1 year
- Challenged to 53- and 400-mg OFCs after OIT cessation x 2 weeks
- Results: 88% reached 53 mg; 69% passed 53-mg challenge (9% in control group) and 25% passed 400-mg challenge (0% in control group)
  - No epinephrine use during treatment (safer than the authors’ prior publication with high-dose OIT)

TAKE HOME POINTS:
- Low-dose OIT may be safer than high-dose OIT
- Low-dose OIT may provide protective threshold but unlikely to allow for ad lib ingestion after 1 year of therapy
**Oral Immunotherapy + Omalizumab**

**Determinants of omalizumab dose-related efficacy in oral immunotherapy: Evidence from a cohort of 181 patients**


- **TAKE HOME POINTS:**
  - Omalizumab may be useful in combination with OIT
  - Dosing used for OIT should rely on weight independent of total IgE rather than those used for treatment of asthma (total IgE:weight)

**Oral Immunotherapy**

**Patient Characteristics and Risk Factors for Home Epinephrine-Treated Reactions During Oral Immunotherapy for Food Allergy**


- Milk OIT risk factor for epinephrine treated reactions at home and treatment failure
  - **Predictors of worse outcome:** Asthma, pre-OIT reaction severity, lower threshold dose at entry, and epinephrine-treated reactions during up-dosing

**Five-year follow-up of early intervention peanut oral immunotherapy**


- 27/29 responders (10 completers did not respond) were eating PN
  - **2 no longer eating:** 1 with EoE, 1 taste aversion

**Long-term outcomes of peanut immunotherapy in children**


- F/up of 17 patients enrolled in OIT or SLIT trial
- 11/17 eating peanut; others avoiding
- QoL improved in parents but mixed in children
**Oral Immunotherapy**

**Induction of sustained unresponsiveness after egg oral immunotherapy compared to baked egg therapy in children with egg allergy**


- Egg desensitization after 2 years > in egg OIT (18/20) compared to BE (4/19) and SU > in egg OIT (10/18) compared to BE (3/4).
- SU achieved in only 17.5% of BE reactive subjects who received egg OIT.
- In patients who are BE-tolerant, egg OIT appears superior to BE ingestion for inducing SU.

**A 5-year summary of real-life dietary egg consumption after completion of a 4-year egg powder oral immunotherapy (eOIT) protocol**


- 30/32 who received eOIT were able to introduce baked egg and 23 who received eOIT were able to introduce concentrated egg; Only 2 subjects were fully restricting egg 5 years after completion of eOIT, compared to 4/11 receiving placebo.
- In the majority of children with egg allergy, treatment with a 4-year eOIT protocol allows for successful introduction of egg.

**Sustained successful peanut oral immunotherapy associated with low basophil activation and peanut-specific IgE**


- BAT and PN-specific Igs may help predict treatment outcome and differentiate desensitization vs SU after OIT.

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**Epicutaneous Immunotherapy (EPIT)**

**Long-term, open-label extension study of the efficacy and safety of epicutaneous immunotherapy for peanut allergy in children: PEOPLE 3-year results**


- At month 36, 51.8% (73/141) of subjects reached eliciting dose ≥ 1000 mg compared with 40.4% at month 12.
- 75.9% experienced an increase in eliciting dose from baseline.
- 13.5% tolerated the full DBPCFC of 5444 mg.
- Median CRD increased from 144 mg to 944 mg.
**Epicutaneous Immunotherapy**

**Sustained unresponsiveness to peanut after long-term peanut epicutaneous immunotherapy**

- After at least 2 years of peanut EPIT, 20/25 (80%) retained protection against 1440 mg of peanut protein after 2 months of avoidance

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**Improvements in Quality of Life in Children Following Epicutaneous Immunotherapy (EPIT) for Peanut Allergy in the PEPITES and PEOPLE Studies**

- QoL measured in 356 patients participating in Phase 3 EPIT trials (PEPITES (blinded) and PEOPLE (open-label))
- **TAKE HOME POINTS:**
  - FAQL improved in patients experiencing increase in eliciting dose independent of whether or not primary endpoint was met

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**Treatment**

**Sialylation of immunoglobulin E is a determinant of allergic pathogenicity**

- Total and allergen-specific IgE do not reproducibly correlate with allergic disease
- Examined glycosylation patterns of total IgE from individuals with peanut allergy
- Analysis revealed increase in sialic acid content on total IgE from individuals with PNA
- Removal of sialic acid from IgE attenuates effector cell degranulation and anaphylaxis
- **TAKE HOME POINTS:**
  - Sialic acid content distinguished PNA from non-atopic (could lead to improved diagnostics)
  - Removing sialic acid from IgE attenuated allergic reactions (potential therapeutic target)
Treatment

Improvements in Dysphagia and Pain With Swallowing in Patients With Eosinophilic Esophagitis Receiving Budesonide Oral Suspension


- Secondary analysis of data from a Phase 2 trial of patients (11-40 y/o) who received BOS (2 mg BID) for EoE
- **TAKE HOME POINT:**
  - BOS (budesonide oral suspension) can reduce dysphagia and pain in patient with EoE

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Treatment

Long-term Efficacy and Tolerability of RPC4046 in an Open-Label Extension Trial of Patients With Eosinophilic Esophagitis


- RPC4046 is a mAb against IL-13
- Study reports results from 52-week, open-label, long-term extension
- **TAKE HOME POINT:**
  - Long-term treatment with anti-IL13 is well-tolerated and may result in histologic and symptomatic improvement for as many as 2/3rd of adults with EoE
Eosinophilic Esophagitis

Efficacy of Epicutaneous Immunotherapy in Children With Milk-Induced Eosinophilic Esophagitis

- 20 children with milk-induced EoE assigned to milk EPIT or placebo (3:1)
- ITT no significant difference, PP participants had significant reduction
- 47% of subjects in open label treatment achieved <15 eos/hpf

An anti-IL-13 antibody reverses epithelial-mesenchymal transition biomarkers in eosinophilic esophagitis: Phase 2 trial results
Hirano I, Dellon ES, Hamilton JD, et al.
J Allergy Clin Immunol 2020; 146:367-76.

- 69 adults with EoE assessed after 16 weeks of anti-IL-13 treatment
- IL-13 inhibition ameliorates both inflammatory and remodeling pathways and could potentially reduce the risk of fibrostenotic complications

Efficacy of Dupilumab in a Phase 2 Randomized Trial of Adults With Active Eosinophilic Esophagitis
Hirano I, Dellon ES, Hamilton JD, et al.

- 47 adults with EoE assessed after 12 weeks of dupilumab
- Reduced dysphagia, and histologic and endoscopic features of the disease compared with placebo.
- Increased esophageal distensibility and was generally well tolerated

Eosinophilic Esophagitis

Budesonide Orodispersible Tablets Maintain Remission in a Randomized, Placebo-Controlled Trial of Patients With Eosinophilic Esophagitis
Gastroenterology 2020; 159:1672-85.

Rapid Recurrence of Eosinophilic Esophagitis Activity After Successful Treatment in the Observation Phase of a Randomized, Double-Blind, Double-Dummy Trial

- 33/58 (57%) of subjects had symptom recurrence within average 244 days of swallowed steroid discontinuation
- Maintenance therapy should be recommended for patients with histologic response to swallowed steroids
Summary

- **Treatment**
  - Daily peanut OIT superior to BIW in first 2 years of treatment
  - Egg OIT > baked egg ingestion in baked egg tolerant egg allergic children
  - Omalizumab dosing for food allergy may differ from asthma dosing
  - EPIT for peanut allergy resulted in eliciting dose ≥1000 mg for 51% of participants

- **EoE**
  - Anti-IL13, Anti-IL4rα, & budesonide ODTs appear promising
Joint ACAAI/AAP SOAI Session
7 for 11: Hot Topics in Pediatric A&I

Anaphylaxis

Julie Wang, MD
Professor of Pediatrics
November 6, 2021

Objectives

• Discuss key updates on pediatric anaphylaxis
Anaphylaxis Prevalence in Children

Rate of epinephrine use for community reactions is low

- Low rates of pre-EMS epinephrine use for anaphylaxis from any cause – range from 1.4 - 74.7% (20 studies)
  - 5 US studies: mean pre-EMS epi use = 26.4%

- Pre-hospital epinephrine use was significantly higher for children vs adults (20.98% vs 7.17%, p=0.0027)
Biphasic reactions occurs in 4%

- Pooled estimate of biphasic reactions = 3.92% (95% CI, 2.88, 5.32)
- Delayed epinephrine associated with risk of biphasic reaction
  - Median time from symptoms onset to first epinephrine dose was longer for those with biphasic reactions (78 vs 45 min, p=0.005)
- First epinephrine dose in ED and delay of 30 min between symptom onset and epinephrine dose were associated with biphasic reactions (OR 3.72 and 3.39, respectively)

Epinephrine availability is a barrier

- Epinephrine prescription rates – North American studies show range of 23.6 - 45.74%
- Factors influencing Rx
  - History of previous reactions to the allergen
  - High parental anxiety
  - Nut allergy
- No difference in prescribing patterns between allergists vs generalists
Epinephrine undertreatment

- Single center study (SickKids ED, Canada) – 368 cases retrospectively validated as anaphylaxis
- 90.8% correctly diagnosed as anaphylaxis in ED
- 76.3% received epinephrine (37.3% treated with epinephrine in ED)
- Predictors for no epinephrine given
  - Anaphylaxis occurring at home (78 vs 60%)
  - First allergic reaction (42.5 vs 22.8%)
  - Mild reaction (23 vs 10.8%)

Predictors for epinephrine treatment

- Independent predictors for appropriate epinephrine use:
  - Reaction at school (aOR 10.3, 95% CI 1.3-78.6; p=0.02)
  - Arrival via EMS (aOR 2.09, 95% CI 1.0-4.0; p=0.02)
Many barriers to epinephrine use

Survey – 164 caregivers previously prescribed epinephrine autoinjectors for their child, asked details of their most severe reaction

<table>
<thead>
<tr>
<th>Reason for Not Using Epinephrine</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms did not seem severe enough</td>
<td>35 (47.9)</td>
</tr>
<tr>
<td>First reaction</td>
<td>30 (41.1)</td>
</tr>
<tr>
<td>Used other medication instead</td>
<td>26 (35.6)</td>
</tr>
<tr>
<td>Caregiver scared/nervous about reaction</td>
<td>21 (28.8)</td>
</tr>
<tr>
<td>Close to hospital or doctor</td>
<td>12 (16.4)</td>
</tr>
<tr>
<td>Not nervous or scared, but did not want to give</td>
<td>8 (11.0)</td>
</tr>
<tr>
<td>Other (patient-specific scenarios)</td>
<td>7 (9.6)</td>
</tr>
<tr>
<td>On way to hospital or doctor</td>
<td>6 (8.2)</td>
</tr>
<tr>
<td>Concerned about adverse effects</td>
<td>5 (6.8)</td>
</tr>
<tr>
<td>Do not like to give child medication</td>
<td>5 (6.8)</td>
</tr>
<tr>
<td>Child scared or nervous about needle</td>
<td>3 (4.1)</td>
</tr>
<tr>
<td>Did not know when to use</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Did not want to go to emergency department</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Caregiver not with child</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Did not want to call 911</td>
<td>1 (1.4)</td>
</tr>
</tbody>
</table>


Multiple epinephrine doses

- Meta-analysis included 86 studies, >36,000 anaphylaxis events
- **50.4%** anaphylaxis reactions treated with epinephrine
- More than 1 dose epinephrine: **7.7%** (95% CI, 6.4-9.1) of anaphylaxis from any trigger were treated with >1 dose epinephrine
- 3 or more epi doses = **2.2%** (95% CI, 1.1-4.1)
- Based on aggregate data, not individual patient data so reasons for multiple doses is not known
  - Possible reasons include reaction progression, underdosing, error in administration, delayed administration or biphasic reaction

Anaphylaxis Severity Grading

Severity grading system for acute allergic reactions

<table>
<thead>
<tr>
<th>Severity grade</th>
<th>Clinical criteria (sub-grading system)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life threatening</td>
<td>Cardiovascular, Neurologic, Respiratory</td>
</tr>
<tr>
<td>ANY Severe</td>
<td>Cardiovascular, Neurologic, Respiratory OR Severe, Gastrointestinal, Mucosal Angioedema</td>
</tr>
<tr>
<td>ANY Moderate</td>
<td>Cardiovascular, Neurologic, Respiratory OR Moderate, Gastrointestinal, Mucosal Angioedema</td>
</tr>
<tr>
<td>ANY Mild</td>
<td>Moderate, Gastrointestinal, Mucosal Angioedema</td>
</tr>
<tr>
<td>ANY Allergic</td>
<td>Anaphylactoid</td>
</tr>
</tbody>
</table>

Symptoms:
- Infants: mottling, cyanosis
- Infants: new onset hypotonia
ED Triage Impacts Anaphylaxis Care

- 1090 ED patients who met NIAID/FAAN criteria for anaphylaxis at the Mayo Clinic between 2010-2018
- Patients triaged using the Emergency Severity Index (ESI)


Severity grading system for acute allergic reactions (Pocket Guide)

<table>
<thead>
<tr>
<th>Severity grades*</th>
<th>Clinical criteria examples (see sub-grading system for complete criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 ANY Severe: Cardiovascular, Neurologic, Respiratory</td>
<td>Cardiovascular: anaphylactic shock, cardiac arrest; Infants: hypotension Neurologic: Glasgow Coma Scale (GCS; <a href="https://www.mdcalc.com/glasgow-coma-score-gcs">https://www.mdcalc.com/glasgow-coma-score-gcs</a>) &lt; 13, seizure; Infants: hypotonia Respiratory: respiratory failure, stridor with increased work of breathing (WOB), bronchospasm with minimal/no air movement and increased WOB</td>
</tr>
<tr>
<td>4 ANY Moderate: Cardiovascular, Neurologic, Respiratory OR Severe: Mucosal/angioidema</td>
<td>Cardiovascular: hypotension, syncope; Infants: mottling, cyanosis Neurologic: GCS 13-14; Infants: lethargic Respiratory: new onset persistent cough, hypoxemia, increased WOB (+/- wheezing), stridor w/o increased WOB Mucosal/angioidema: severe oropharyngeal (tongue/palate/uvula) swelling</td>
</tr>
<tr>
<td>3 ANY Mild: Cardiovascular, Neurologic, Respiratory</td>
<td>Cardiovascular: weak, dizzy, palpitations; Infants: tachycardia not related to other causes such as crying, discomfort, or medications Neurologic: confusion, drowsy; Infants: unexplained irritability, decreased activity Respiratory: dyspnea, chest tightness; new onset cough, wheezing w/o increased WOB</td>
</tr>
<tr>
<td>2 2 or more Mild, ANY Moderate: Skin, Gastrointestinal, Mucosal/angioidema</td>
<td>Skin: Mild: localized urticaria, erythema; Moderate: generalized urticaria, erythema Gastrointestinal: Mild: 1-2 episodes of emesis/diarrhea; Moderate: ≥ 3 episodes of emesis/diarrhea Mucosal/angioidema: Mild: facial swelling, rhinorrhea; Moderate: moderate oropharyngeal swelling</td>
</tr>
<tr>
<td>1 ANY Mild: Skin, Gastrointestinal, Mucosal/angioidema</td>
<td>Skin: localized urticaria, erythema Gastrointestinal: 1-2 episodes of emesis or diarrhea Mucosal/angioidema: facial swelling, rhinorrhea</td>
</tr>
</tbody>
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Higher Acuity Patients More Often Received Epinephrine

<table>
<thead>
<tr>
<th></th>
<th>Higher acuity (level 1 or 2) N=541</th>
<th>Lower acuity (level 3 or 4) N=549</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received epinephrine</td>
<td>53%</td>
<td>40%</td>
</tr>
<tr>
<td>Time to epinephrine (median)</td>
<td>13 min</td>
<td>28 min</td>
</tr>
</tbody>
</table>


Factors associated with acuity level

• Lower acuity more likely if chief concern was dermatologic (hives, rash, pruritus) – OR 2.33, 95% CI 1.20-4.53

• Less likely to be assigned lower acuity level:

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>0.43</td>
<td>0.31-0.60</td>
</tr>
<tr>
<td>EMS gave epinephrine</td>
<td>0.56</td>
<td>0.38-0.82</td>
</tr>
<tr>
<td>Posterior pharyngeal or uvular angioedema</td>
<td>0.56</td>
<td>0.38-0.82</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>0.34</td>
<td>0.18-0.64</td>
</tr>
<tr>
<td>Increased HR</td>
<td>0.83</td>
<td>0.73-0.95</td>
</tr>
<tr>
<td>Increased RR</td>
<td>0.70</td>
<td>0.60-0.82</td>
</tr>
</tbody>
</table>

Summary

- Prevalence of anaphylaxis continues to rise, but prevalence varies by age
- Epinephrine continues to be under-used, both in the community and medical settings
- A number barriers have been identified, for patients/caregivers and clinicians
- A new severity grading system has been developed

Thank you!
Immunology

Mary Beth Fasano, MD, MSPH, FAAAI, FACAAI
Professor Clinical Medicine & Pediatrics
University of Iowa Hospitals & Clinics

Gene Therapy: ADA-SCID

- 50 patients with ADA-SCID
  - 2 U.S. studies
    - 30 patients
    - Fresh & cryopreserved formulations
    - 24 mon follow-up
  - U.K. study
    - 20 patients
    - Fresh formulation
    - 36 mon follow-up
Patients & Study Procedures

U.S. study sites
- Age 1 mon or older
- No HLA-matched sibling or related donor

Nonmyeloablative busulfan conditioning

CD34+ HSPCs transduced with EFS-ADA LV

Received PEG-ADA from diagnosis until 30 days post treatment


Key Study Findings

- Kaplan-Meier Curves for Event-free Survival
  - Overall survival = 100%

- Event-free survival at 12 months
  - U.S. studies = 97%
  - U.K. study = 100%

- Persistent engraftment
  - U.S. studies = 29 of 30 patients
  - U.K. study = 19 of 20 patients

- Sustained metabolic detoxification & normalization of ADA activity levels

- Robust immune reconstitution

- Safety
  - No monoclonal expansion, leukoproliferative complications or emergence of replication-competent lentivirus
  - No autoimmunity or GVHD
  - Most adverse events were low grade

Retrospective chart review of 80 patients diagnosed with CGD over 20 years
5 (6.25%) had evidence of HLH per 2004 criteria

Important study observations

TABLE I. Clinical and laboratory parameters of children with chronic granulomatous disease and hemophagocytic lymphohistiocytosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at diagnosis</th>
<th>Type of CGD</th>
<th>Sex</th>
<th>Molecular diagnosis</th>
<th>Associated Infection</th>
<th>Minilob</th>
<th>TC</th>
<th>IgG</th>
<th>IgA</th>
<th>IgM</th>
<th>Bone marrow</th>
<th>SFT (g/L)</th>
<th>SGPT (U/L)</th>
<th>Ferritin (ng/ml)</th>
<th>TSH (mU/L)</th>
<th>Thyroid (ug/dl)</th>
<th>Treatment Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>40 d</td>
<td>XL</td>
<td>M</td>
<td>CSBP c.306G&gt;A, p.Tyr43His</td>
<td>Sphingobacterium</td>
<td>70</td>
<td>6.5</td>
<td>2.36</td>
<td>0.34</td>
<td></td>
<td></td>
<td>3100</td>
<td>1800</td>
<td>6490</td>
<td>0.6</td>
<td>35,200</td>
<td>Died</td>
</tr>
<tr>
<td>Case 2</td>
<td>3 mo</td>
<td>XL</td>
<td>M</td>
<td>CSBP c.306G&gt;A, p.Tyr43His</td>
<td>Sphingobacterium</td>
<td>70</td>
<td>6.5</td>
<td>2.36</td>
<td>0.34</td>
<td></td>
<td></td>
<td>3100</td>
<td>1800</td>
<td>6490</td>
<td>0.6</td>
<td>35,200</td>
<td>Died</td>
</tr>
<tr>
<td>Case 3</td>
<td>2 y 2 mo</td>
<td>XL</td>
<td>M</td>
<td>CSBP c.306G&gt;A, p.Tyr43His</td>
<td>Sphingobacterium</td>
<td>70</td>
<td>6.5</td>
<td>2.36</td>
<td>0.34</td>
<td></td>
<td></td>
<td>3100</td>
<td>1800</td>
<td>6490</td>
<td>0.6</td>
<td>35,200</td>
<td>Died</td>
</tr>
<tr>
<td>Case 4</td>
<td>2 y 2 mo</td>
<td>XL</td>
<td>M</td>
<td>CSBP c.306G&gt;A, p.Tyr43His</td>
<td>Sphingobacterium</td>
<td>70</td>
<td>6.5</td>
<td>2.36</td>
<td>0.34</td>
<td></td>
<td></td>
<td>3100</td>
<td>1800</td>
<td>6490</td>
<td>0.6</td>
<td>35,200</td>
<td>Died</td>
</tr>
<tr>
<td>Case 5</td>
<td>10 mo</td>
<td>AR</td>
<td>M</td>
<td>JUP2 c.351,366delAC, p.Thr379Phe,380delG</td>
<td>Peptostreptococcus</td>
<td>90</td>
<td>14.0</td>
<td>1.87</td>
<td>0.27</td>
<td></td>
<td></td>
<td>3100</td>
<td>1800</td>
<td>6490</td>
<td>0.6</td>
<td>35,200</td>
<td>Died</td>
</tr>
</tbody>
</table>


Key study conclusions

- HLH must be considered in children with CGD when they have multisystem dysfunction and progressively worsening cytopenias.
- Work-up for CGD must be considered in children with HLH especially when they have associated infections or a suggestive family history.
- The frequency of HLH in association with CGD is unknown (likely rare) with only 36 such cases reported to date.
- The exact reasons why these children are prone to HLH are unclear.

Prevalence, risk factors & clinical significance of hypogammaglobulinemia following rituximab therapy in children

- Multicenter, retrospective cohort study (Montreal, Halifax, Boston, Auckland)
  - 207 patients; median age = 12.0 years
  - Rituximab for any reason with ≥1 yr of follow-up after 1st dose
  - 4 doses of 375 mg/m² on average
  - Excluded if prior diagnosis of PID or h/o rituximab after HSCT

Hypogammaglobulinemia pre/post rituximab

- Normal Ig levels pre-rituximab
  - 31.0% developed low IgG
  - 13.5% developed low IgA
  - 55.0% developed low IgM

- Mean IgM decreased as early as 6 months post-rituximab
  - IgA levels least frequently affected by rituximab

- CD19+ B-cell lymphopenia in 17/43 (39.5%) at median follow-up of 22.2 months; 7/11 (63.6%) had persistent low IgG


Infection risk post-rituximab therapy

- 49/207 patients (23.7%) developed serious infections requiring ED visit and/or hospitalization
  - Low IgG post-rituximab associated with significant ↑ risk for infection
  - Use of prednisone or other immunosuppressive meds NOT independently associated with ↑ infection rate


- Hypogammaglobulinemia post-rituximab is frequently seen in children
- Low IgG levels are associated with significant increase in serious infections
- Underlying PIDs are relatively common in children receiving rituximab

**STING-Associated Vasculopathy with Onset in Infancy (SAVI)**


- Type I interferonopathy
- GOF mutations in STING1

**Cohort of 21 patients (17 families)**
- Median age of onset = 8.5 months
- FTT common
- Skin disease in 86%
  - 29% we severe skin vasculopathy involving nose, cheeks, fingers, toes
SAVI associated lung disease and other clinical/immunologic features

- Pulmonary disease associated with high degree of disability & mortality
  - Onset in infancy/early childhood
- Immunologic features
  - Autoantibodies in 20 of 21 patients
  - ↑IgG & ↑IgA in 20 of 21 patients
  - Mild CD3⁺ & CD4⁺ T-cell lymphopenia
  - Memory CD8 lymphopenia
- Treatment with JAK inhibitors
  - Ruxolitinib → improvement in fever, lung & skin disease


Key highlights regarding SAVI


- Lung disease was constant, leading to early & insidious development of fibrosis
- Polyarthritis with +RF is frequent
- Consider careful clinical & genetic screening of patients with early onset, apparently isolated skin, lung, or joint inflammation, with presence of autoantibodies or memory CD8 lymphopenia
- JAK inhibitors are a promising treatment with early diagnosis needed to maximize treatment benefit
The coronavirus drawings of 94 children of the 103 who participated in the study (9 did not consent to their drawing being published).
Implications for Practice

• Gene therapy may be a robust/viable treatment option for ADA-SCID
• HLH can be the presenting manifestation of CGD; consider work-up for CGD in infants & young children presenting with HLH
• Assess Ig levels before & after rituximab initiation; consider Ig replacement when IgG is low; consider PID screening in patients with autoimmune cytopenias
• Consider SAVI in infants/young children with skin, lung, or joint inflammation in the presence of autoantibodies or memory CD8 lymphopenia
Epidemiology
Ruchi Gupta, MD, MPH
Professor of Pediatrics & Medicine, Northwestern University Feinberg School of Medicine
Clinical Attending, Ann & Robert H. Lurie Children’s Hospital of Chicago
Director, Center for Food Allergy & Asthma Research

Objectives

• To characterize pediatric food allergy prevalence in the U.S.

• To characterize adult food allergy prevalence in the U.S.
### Prevalence of Pediatric Food Allergy Around the World

#### North America
- **Canada**: 7.1% (Soler 2012) (0-17 yr)
- **Mexico**: 3.0% (Guevara 2016) (0-17 yr)
- **USA**: 5.6% (Gupta 2016) (5-13 yr)

#### Central America & South America
- **Brazil**: 0.6% (Carvalhe 2016) (4-59 mo)
- **Chile**: 5.5% (Monos 2014) (5-15 yr)
- **El Salvador**: 5.3% (Carreras-Chavez 2016) (4-12 yr)

#### Middle East
- **Israel**: 3.6% (Sorek 2017) (13-14 yr)
- **Kuwait**: 5.4% (Ali 2017) (17-30 yr)
- **Lebanon**: 4.1% (Sawalha 2018) (6-17 yr)
- **Turkey**: 0.8% (Ozkan 2009) (6-9 yr)
- **UAE**: 8.0% (Al Hammadi 2010) (6-9 yr)

#### Europe
- **Austria**: 1.7% (Baehr 2007) (0-17 yr)
- **Belgium**: 4.9% (Reperant 2013) (0-17 yr)
- **Croatia**: 9.4% (Grujicic 2015) (0-6 yr)
- **Denmark**: 3.6% (Wisborg 2007) (0-6 yr)
- **Finland**: 9.3% (Pyrhonen 2009) (1-4 yr)
- **France**: 4.7% (March 2009) (2-14 yr)
- **Germany**: 3.5% (Gruner 2008) (0-17 yr)
- **Greece**: 2.0% (Lyons 2020) (7-10 yr)
- **Greenland**: 4.1% (Rocha 2018) (5-10 yr)
- **Iceland**: 1.2% (Reid 2004) (7-10 yr)
- **Italy**: 3.9% (Maggi 2001) (0-17 yr)
- **Lithuania**: 3.0% (Petru 2012) (7-10 yr)
- **Malta**: 2.5% (Carvalho 2016) (6-6 yr)
- **Netherlands**: 3.0% (Beckers 2008) (7-10 yr)
- **Norway**: 6.8% (Weihrauch 2008) (2 yr)
- **Poland**: 5.6% (Leyko 2010) (7-10 yr)
- **Portugal**: 5.7% (Gaspar-Maques 2011) (0-6 yr)
- **Slovenia**: 4.5% (Gruner 2008) (0-17 yr)
- **Spain**: 3.5% (Aran 2007) (7-10 yr)
- **Sweden**: 5.8% (Fotakis 2016) (16 yr)
- **Switzerland**: 2.3% (Leporini 2014) (7-10 yr)
- **UK**: 3.0% (Soler 2008) (3 yr)

#### Africa
- **Ghana**: 5.0% (Opoku 2011) (5-16 yr)
- **South Africa**: 1.8% (Duma 2010) (1-3 yr)

#### Asia & Oceana
- **Australia**: 3.9% (Hadi 2017) (4 yr)
- **China**: 7.7% (Hu 2010) (0-2 yr)
- **Hong Kong**: 4.8% (Wong 2017) (0-14 yr)
- **Japan**: 5.1% (Ezoe 2017) (0-17 yr)
- **Singapore**: 5.4% (Loo 2014) (11-30 mo)
- **South Korea**: 4.1% (Kim 2011) (6-16 yr)
- **Taiwan**: 7.4% (Wu 2012) (0-16 yr)
- **Thailand**: 1.1% (Lak-Araya 2011) (3-7 yr)

*(range of ages comprising study sample)*
National Trends in Food Allergy

Rates of food-induced anaphylaxis are increasing in the US

*Data from the Healthcare Cost and Utilization Project Kids’ Inpatient Database, the only all-payer pediatric inpatient care database in the United States.


The Economic Impact of Childhood Food Allergy in the United States

Overall Economic Cost
$24.8 Billion

Direct Medical Costs
$4.3 Billion

Family Cost
$20.5 Billion
$4,184/year per allergic child

The Public Health Impact of Parent-Reported Childhood Food Allergies in the United States

Ruchi S. Gupta, MD, MPH,a,b,1,4,5 Christopher M. Warren, BA,a Bridget M. Smith, PhD,a,f Jesse A. Blumenstock, BS,a Jialing Jiang, BA,a Matthew M. Davis, MD, MAPP,b,c,e,f Kari C. Nadeau, MD, PhD,a

Survey Administration Methods

- Administered between October 2015 and September 2016 to a representative sample of >40,000 US households.

- A dual-sample approach was utilized through probability-based AmeriSpeak panel and non-probability-based SSI sample

- Point prevalence estimates were driven by the nationally-representative AmeriSpeak respondents, while the SSI sample helped to ensure sufficient precision when analyzing subpopulations.

Childhood Food Allergy Prevalence in the US

8% of US children have a food allergy

~ 2 kids per classroom

Of children who have a food allergy, 40% are allergic to multiple foods

42% have experienced a severe reaction
Overall Convincing FA Prevalence = 7.6% (7.1%-8.1%)
Overall Physician-diagnosed FA Prevalence = 4.7% (4.3%-5.0%)


Northwestern Medicine
Feinberg School of Medicine
Age
Food Allergen Prevalence by Age
Among Children with Food Allergy

Food-allergic Children with Top 9 Allergies by Age
### Age-specific Prevalence of Convincing Food Allergy among US Children

![Graph showing age-specific prevalence of convincing food allergy among US children.](image)


---


Multiple Food Allergies

Parent-reported Pediatric FA Prevalence = 11.4% (95% CI: 10.8%-12.0%)
Convincing Pediatric FA Prevalence = 7.6% (95% CI: 7.1%-8.1%)
Physician-Confirmed FA Prevalence = 4.7% (95% CI: 4.3%-5.0%)
Patterns of Convincing Multi-Food Allergy Among US Children

<table>
<thead>
<tr>
<th>Peanut</th>
<th>Tree Nut</th>
<th>Sesame</th>
<th>Milk</th>
<th>Egg</th>
<th>Fin Fish</th>
<th>Shellfish</th>
<th>Soy</th>
<th>Wheat</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>61</td>
<td>55</td>
<td>15</td>
<td>29</td>
<td>38</td>
<td>25</td>
<td>33</td>
<td>22</td>
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<tr>
<td>33</td>
<td>100</td>
<td>44</td>
<td>9</td>
<td>18</td>
<td>24</td>
<td>14</td>
<td>24</td>
<td>18</td>
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<td>5</td>
<td>8</td>
<td>100</td>
<td>3</td>
<td>6</td>
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<td>5</td>
<td>11</td>
<td>13</td>
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<tr>
<td>13</td>
<td>15</td>
<td>23</td>
<td>100</td>
<td>35</td>
<td>15</td>
<td>11</td>
<td>37</td>
<td>43</td>
</tr>
<tr>
<td>12</td>
<td>13</td>
<td>26</td>
<td>17</td>
<td>100</td>
<td>20</td>
<td>11</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>9</td>
<td>11</td>
<td>23</td>
<td>4</td>
<td>12</td>
<td>100</td>
<td>24</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>15</td>
<td>15</td>
<td>31</td>
<td>7</td>
<td>16</td>
<td>57</td>
<td>100</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>26</td>
<td>9</td>
<td>13</td>
<td>12</td>
<td>7</td>
<td>100</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>31</td>
<td>11</td>
<td>12</td>
<td>11</td>
<td>8</td>
<td>27</td>
<td>100</td>
</tr>
</tbody>
</table>

(% of children with convincing column allergy who are also allergic to the row allergen)

Pediatric Clinical Outcomes
By Number of Current Convincing Food Allergies

- ≥ 1 FA-related ED visits in past 12 months
- ≥ 1 Lifetime FA-related ED visit
- ≥ 1 FA with Severe Reaction History
- Has Current EAI Prescription
- Reports previous EAI use to treat FA reaction
Childhood Food Allergy Severity

42.3% of food-allergic kids reported a history of 1+ severe reaction

% of Children with Convincing FA Reporting Severe Reaction History

- Peanut: 59.2%
- Any Tree Nut: 56.1%
- Any Shellfish: 48.7%
- Fin Fish: 49.0%
- Soy: 36.8%
- Wheat: 36.7%
- Sesame: 27.2%
- Egg: 28.1%
- Milk: 25.3%
Emergency Department Visits
Among Children with Food Allergy

- 1+ Lifetime ED Visit
- No Lifetime ED Visits

- 1+ Past Year ED Visit
- No ED Visits in Past Year

Parent-Reported Reaction History
FARE National Patient Registry

- Average Number of Reactions
- Perceived Severity of Most Recent Reaction


Disparities in Food Allergy
Racial Differences in Frequency of FA-related ED Visits

ED Visits in Lifetime

<table>
<thead>
<tr>
<th></th>
<th>White NH</th>
<th>Black NH</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Children with FA</td>
<td>37.3</td>
<td>47.3</td>
<td>48.2</td>
</tr>
</tbody>
</table>

P-value: 0.02

ED Visits in Previous 12 Mo

<table>
<thead>
<tr>
<th></th>
<th>White NH</th>
<th>Black NH</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Children with FA</td>
<td>15.5</td>
<td>23.6</td>
<td>21.9</td>
</tr>
</tbody>
</table>

P-value: 0.23

p<.05 for Lifetime Visits

FA by Race/Ethnicity
Food Allergies by Race/Ethnicity

- Black children have higher rates of current food allergy than children of any other racial/ethnic background.

Reported Convincing Food Allergy Among US Children

- Black, Non-Hispanic Children: Significantly higher rates of peanut, egg, shellfish, and finfish allergy.
- Asian, Non-Hispanic Children: Significantly higher rates of tree nut.
Rates of physician-diagnosed atopic conditions were significantly higher among children with convincing FA compared with other children.

<table>
<thead>
<tr>
<th>Physician Diagnosed Co-Morbid Conditions</th>
<th>All Children</th>
<th>Children with FA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>12.2 (11.4–13.0)</td>
<td>32.6 (29.5–35.9)*</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Atopic Dermatitis</td>
<td>5.9 (5.3–6.5)*</td>
<td>14.9 (12.5–17.7)*</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Eosinophilic Esophagitis (EoE)</td>
<td>0.2 (0.10–0.2)*</td>
<td>0.7 (0.4–1.1)*</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Allergic Rhinitis</td>
<td>12.8 (12.0–13.6)*</td>
<td>30.4 (27.6–33.4)*</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Other Chronic Condition</td>
<td>4.2 (3.7–4.7)*</td>
<td>10.1 (8.2–12.3)*</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>
Prevalence of Lifetime Physician-diagnosed EoE

USA population: 330 million
Survey of 53,575 households

≈ 120,000 US Children with EoE
(0.16% of US Pediatric Population)

≈ 450,000 US Adults with EoE:
(0.18% of US Adult population)

EoE = Eosinophilic Esophagitis

Adult Population
Adult Food Allergy Severity

51.1% of food-allergic adults reported a history of 1+ severe reaction.
More adults developing food allergies but many go undiagnosed

More adults than children have food allergies and a new study suggests there's more to learn.

**Doctors Surprised by Scope of Adult-Onset Food Allergies**

New research found nearly 12% of U.S. adults have food allergies, more than many doctors anticipated.

**Food Allergies in Adults**

More than 10% of U.S. adults — or more than 26 million people — have a history of food allergy.

**Peanut allergies affect over 4.6 million adults in the US, study finds**


**Racial Disparities**
The FORWARD Study

- First NIH R01 Study examining racial differences in FA burden
- Enrolling 1000 families at 4 sites through 2020 (Currently at 350 Black, 450 White families)
- Recently received NIAID supplement to expand recruitment to Hispanic/Latinx families
- 4 sites:

Cincinnati Children’s Hospital
Dr. Amal H. Assa’ad

DC Children’s National
Dr. Hemant Sharma

Rush University Medical Center
Dr. Mary Tobin

Lurie Children’s Hospital
Dr. Ruchi Gupta

Prevalence of Top 9 FA in FORWARD Cohort

Mahdavinia M, Tobin MC, Fierstein JL, et al. Black children have a higher rate of shellfish allergy associated with increased asthma risk. Annals of Allergy, Asthma, & Immunology. 2020 (Under Review)
Connect With CFAAR

Website: cfaar.northwestern.edu
Instagram: @cfaarnu
Twitter: @cfaarnu
Facebook: Center for Food Allergy & Asthma Research (@cfaarnu)
Email: cfaar@northwestern.edu

(Extra Slides)
List of Stringent Symptoms Indicative of Convincing Food Allergy

- Skin symptoms:
  - Hives
  - Itching
  - Rash
  - Swelling (except lip/tongue swelling)
  - Other:

- Mouth/Throat Symptoms
  - Lip/tongue swelling
  - Difficulty swallowing
  - Hoarse voice
  - Itchy mouth
  - Throat tightening
  - Mouth or throat tingling
  - Other:

- Breathing Symptoms
  - Chest tightening
  - Nasal congestion
  - Repetitive cough
  - Trouble breathing
  - Wheezing
  - Other:

- Gastrointestinal (GI) Symptoms
  - Belly pain
  - Cramps
  - Diarrhea
  - Nausea
  - Vomiting
  - Other:

- Cardiovascular/Heart Symptoms
  - Chest pain
  - Rapid heart rate
  - Fainting, dizziness, or feeling light headed
  - Low blood pressure
  - Other:

- Other Symptoms
  - Anxiety
  - Feeling of impending doom
  - Headache
  - Other:

- Additional symptoms (Please describe):

Symptoms in bold italics comprised our expert panel’s stringent symptom list.
The presence of at least one stringent symptom was required during a child’s most severe reaction to a given food in order to classify each parent-reported food allergy as “convincing.”

Stringent Food Allergy Classification Protocol

1. **Reported Symptom ≠ Stringent Symptom**
   - No convincing history of FA

2. **Stringent symptoms = Hives, swelling (except lip/tongue), lip/tongue swelling, difficulty swallowing, throat tightening, chest tightening, trouble breathing, wheezing, vomiting, chest pain, rapid heartbeat, fainting, low blood pressure**
   - NOTE: GI symptoms commonly associated with intolerance (except vomiting) ≠ stringent symptom

3. **Allergens Commonly Associated with OAS**
   - AND Reported Symptoms = Only Skin/Oral Mucosa Symptoms (Except for Hives)
   - Excluded probable OAS

   - *Allergens commonly associated with OAS = Peanut, Shellfish, Tree Nut, Fin Fish, Wheat, Soy, Barley, Rice, Seed, Spice, Fruit, or Vegetable*

4. **Confirmed FA was diagnosed by a physician**
   - Confirmed FA

5. **Stringent symptoms only reported within a single organ system**
   - Non-Severe Convincing FA

6. **Stringent symptoms reported across multiple organ systems**
   - Severe Convincing FA

Analytic sample:

- **Is there at least one convincing FA symptom?**
  - ≥1 stringent symptom

- **Does reaction history indicate OAS?**
  - No

- **Convincing FA**

- **Was the convincing FA diagnosed by a physician?**

- **Of Convincing and Confirmed FA - Is the FA severe?**
### Economic Burden of Food Allergy

<table>
<thead>
<tr>
<th>Type of Cost</th>
<th>Mean Annual Costs (SE), US$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Direct Costs borne by health care system</td>
<td>≤$50K</td>
</tr>
<tr>
<td>ER and Hospitalization costs*</td>
<td>1347</td>
</tr>
<tr>
<td>Specialist costs**</td>
<td>1021</td>
</tr>
<tr>
<td>Total Out-of-Pocket Costs borne by Families</td>
<td>228</td>
</tr>
<tr>
<td>Medication costs***</td>
<td>3174</td>
</tr>
<tr>
<td>Special foods costs</td>
<td>171</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, ***P<0.001 for F-test of equality of means across groups

### Willingness to Pay and Measure of Actual Cost

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Annual Costs, US$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (in billions)</td>
</tr>
<tr>
<td>WTP</td>
<td>20.8</td>
</tr>
<tr>
<td>Costs borne by families</td>
<td>5.5</td>
</tr>
<tr>
<td>Lost labor productivity</td>
<td>0.77</td>
</tr>
<tr>
<td>Opportunity</td>
<td>14.2</td>
</tr>
<tr>
<td>Total</td>
<td>4.3</td>
</tr>
<tr>
<td>Direct medical costs</td>
<td>20.5</td>
</tr>
<tr>
<td>Reported costs borne by families</td>
<td>24.8</td>
</tr>
</tbody>
</table>
Economic Burden of Food Allergy

<table>
<thead>
<tr>
<th>Type of Cost</th>
<th>White</th>
<th>African American</th>
<th>Hispanic</th>
<th>Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Direct Costs borne by health care system***</td>
<td>999</td>
<td>493</td>
<td>643</td>
<td>885</td>
</tr>
<tr>
<td>ER and Hospitalization costs***</td>
<td>504</td>
<td>108</td>
<td>395</td>
<td>1271</td>
</tr>
<tr>
<td>Specialist costs***</td>
<td>310</td>
<td>157</td>
<td>127</td>
<td>101</td>
</tr>
<tr>
<td>Total Out-of-Pocket Costs borne by Families***</td>
<td>4203</td>
<td>395</td>
<td>1093</td>
<td>1327</td>
</tr>
<tr>
<td>Medication costs***</td>
<td>312</td>
<td>52</td>
<td>148</td>
<td>87</td>
</tr>
<tr>
<td>Special foods costs***</td>
<td>1213</td>
<td>177</td>
<td>219</td>
<td>148</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001 for F-test of equality of means across groups

Income Disparities in Food Allergy

- Low-income families:
  - Spend 2.5x more on **FA ED visits and hospitalizations**
  - Spend less on **specialty** visits
  - Spend less on out-of-pocket costs for **medications**