



Development of Clinical Tolerance in Children with Food Allergy





Presenter:

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Team

Study is done in collaboration with 4 large medical centers:

1. Northwestern University, Ann & Robert H. Lurie Children's Hospital of Chicago
2. Rush University Medical Center
3. Cincinnati Children's Hospital Medical Center
4. Children's National Health Systems

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- Susan Fox, PA-C²
- And more....



Disclosures

- No Personal Disclosures
- This presentation is based on the FORWARD Cohort.
- FORWARD is supported by the NIAID [[R01 AI130348/AI/NIAID NIHHS](#)].

Background

- Food allergy is a potentially life-threatening condition that can significantly affect the quality of life and well-being of patients and their families.
- The rise of IgE-mediated food allergies (FA) in childhood is a growing public health concern.
- In the United States, an estimated 8% children are affected by IgE-mediated food allergies. [Gupta et al., 2011]



Background

- Despite the rising prevalence of food allergies, some children outgrow them.
- However, predictors for the development of clinical tolerance are not well known and understood.
- **There is currently limited data in the literature on the development of clinical tolerance in food allergy.**
- For this reason, we decided to examine factors that may be associated with outgrowing food allergies in children.



Scope of our Analyses

Focus on the development of Clinical Tolerance/Outgrown Food Allergy by analyzing the FORWARD Cohort, one of the largest cohorts of children with FA:

- Investigate sociodemographic factors and comorbidities associated with the development of clinical tolerance in children with food allergy.
- Investigate reaction history and types of food allergens associated with the development of clinical tolerance in children with food allergy.

About FORWARD

FORWARD (Food Allergy Management and Outcomes Related to Racial/Ethnic Differences from Infancy through Adolescence) is a multi-center prospective cohort study aiming now to recruit **1600 parent-child pairs**, including 500 Black participants, 500 White participants, 200 Asian participants, and 400 Hispanic/Latino participants.

This cohort of pediatric patients comes from 4 large medical centers: *Ann & Robert H. Lurie Children's Hospital of Chicago/ Northwestern University, Rush University Medical Center, Cincinnati Children's Hospital Medical Center, and Children's National Medical Center.*



About FORWARD

FORWARD seeks to expand our knowledge and understanding of food allergy using a racially/ethnically and socioeconomically diverse cohort of children with food allergy.



About FORWARD

Participants in the study include children aged 0–12 years from different racial/ethnic backgrounds with IgE-mediated food allergies.



An initial survey is taken at the time of enrollment



Followed by quarterly follow-ups surveys sent to participants.



Trained staff extracts EHR data, including demographics, initial visit summary, follow-up visit summaries, and laboratory testing results for each child participant.

PRELIMINARY ANALYSES

looking at patterns, trends,
relationships within the dataset...
as we recruit more participants
to expand the cohort and
approach new target goals.



ONE-CENTER PRELIMINARY ANALYSIS

EHR Data

- Can children outgrow their food allergies?
- What sociodemographic factors are associated with the development of clinical tolerance?

RUMC PRELIMINARY STUDY Methods

- Data for this analysis focused on 1 study site.
- Data was extracted by research staff from the participants' **Electronic Health Records (EHR)** at Rush University Medical Center (RUMC) using REDCap.
- We compared children who developed oral tolerance to at least 1 food (OT/"Outgrown FA") group to children who did not outgrow any FA (active-FA /"No Outgrown FA") group.
- Food tolerance was reported in the medical record by a physician after successful graded oral challenge in clinic, re-introduction at home or accidental episodes of ingestion.
- **Charts were also independently reviewed by an allergist to ensure fidelity of the extracted data.**
- Chi-square determined associations and t-tests compared mean values between the "**Outgrown Food Allergy**" (FA) group and the "**No Outgrown FA**" group.

RUMC PRELIMINARY STUDY Findings



700 children with a diagnosis of IgE mediated FA were recruited to the FORWARD study across 4 sites.



The cohort at RUMC included 188 children
62% males
51% Non-Hispanic Black children,
32% Non-Hispanic White children,
16% Hispanic children.

RUMC PRELIMINARY STUDY Findings

- **Race/ethnicity was significantly associated with the development of tolerance**

(P = 0.0451)

- *Larger sample size was needed to achieve greater statistical power.*
- *Sample size was small and not well balanced/represented (only 30 Hispanic Children).*

	Sample Characteristic (N = 188)	Outgrown Food Allergy (N = 39)	No Outgrown Food Allergy (N = 149)	P-value
Sex	Female	17	54	0.5110
	Male	22	95	
Race / Ethnicity	Non-Hispanic White	17	44	0.0451*
	Non-Hispanic Black	18	78	
	Hispanic	3	27	
Insurance Type	Medicaid (public)	9	69	0.0170*
	Private	26	63	
	No Reported Insurance	4	16	
Age (Mean)	At Enrollment	5.95 years (SD = 3.76)	6.16 years (SD = 3.72)	t-value = 0.3197, p-value = 0.7503
	At Reporting First Food Allergy	3.27 years (SD = 2.74)	4.18 years (SD = 3.57)	t-value = 1.5889, p-value = 0.1173
	At Reporting First Food Tolerance	5.02 years (SD = 3.32)	NA	NA

P value ≤ 0.05, statistically significant, T value ≥ 1.96 statistically significant

RUMC PRELIMINARY STUDY Findings

- **Insurance coverage (private insurance) was significantly associated with outgrowing FA (P = 0.0170)**
 - **12%** children with Medicaid insurance outgrew food allergies, compared to **29%** of privately insured children.

	Sample Characteristic (N = 188)	Outgrown Food Allergy (N = 39)	No Outgrown Food Allergy (N = 149)	P-value
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	At Reporting First Food Tolerance	5.02 years (SD = 3.32)	NA	NA

P value ≤ 0.05, statistically significant, T value ≥ 1.96 statistically significant

RUMC PRELIMINARY STUDY Findings

- In the tolerance group, the mean age of first reaction to any food was **3.27 years (SD= 2.74)**, which was less than the mean age for those who never developed tolerance (**M= 4.18 years, SD= 3.57**).
- However, this difference was not statistically significant ($t= 1.5889$, $p= 0.1173$), *likely due to a need for a larger sample size to achieve statistical power.*

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P value ≤ 0.05 , statistically significant, T value ≥ 1.96 statistically significant

RUMC PRELIMINARY STUDY Findings

- The mean age for the development of tolerance was **5.02 years** (SD 3.32).
- **39 out of 188 (21%) children outgrew at least 1 FA, with a total of 72 outgrown FA.**
- **Unbaked milk and Unbaked egg were the most frequently outgrown foods.**
 - *Consistent with other studies.*

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P value ≤ 0.05, statistically significant, T value ≥ 1.96 statistically significant

RUMC PRELIMINARY STUDY Findings

TAKE HOME POINTS:

- Food Allergies can be outgrown.
- Most frequently outgrown foods were milk and egg, followed by soy, peanut, tree nuts and wheat.
- **Children with private insurance were more likely to outgrow their food allergies than those with Medicaid insurance. The significant associations between insurance types and outgrowing FA likely point to social determinants of health that influence outcome.**
- Suboptimal follow-up and monitoring of those patients could help explain the differences observed between the “Outgrown FA” group and the “No Outgrown FA group”.

Limitations of this analysis:

- No socioeconomic status (SES) and household income data
- Manual chart review and transcription are susceptible to errors
- Analysis done for 1 site
- Sample size not large enough, not equally represented
- Crude analysis; analysis did not adjust for confounding factors

FOUR CENTERS PRELIMINARY ANALYSIS I

Caregiver-reported Data

What sociodemographic factors and comorbidities are associated with the development of clinical tolerance?

FOUR CENTERS PRELIMINARY STUDY Methods

- Data for this analysis came from all 4 centers.
- **We analyzed results of the intake survey completed by caregivers at enrollment in the study to investigate sociodemographic factors and comorbidities that may be associated with outgrowing food allergy.**
- We compared children who developed oral tolerance to at least 1 food (OT group) to children who did not outgrow any FA (active-FA group).
- Bivariate analysis was carried out using *chi-square statistics*.

FOUR CENTERS PRELIMINARY STUDY Methods

Families who consented to be involved in the study completed an **initial intake survey** that inquired about current food allergies, former food allergies, birth and early life history, comorbidities, family history and other information.



ANALYSIS

DOMAIN	DESCRIPTION
Initial Survey	<ul style="list-style-type: none">• Patient age, sex, birthdate, country of birth, race/ethnicity• Insurance type, home address• Reaction history, allergenic foods, comorbid diagnoses,• parental/sibling atopy, # of children with/without FA,• Parental education, annual household income, household composition etc..
Current FA	# of food allergies, type of food allergens, symptoms, and management after reactions
Former FA	# of outgrown allergies, type of food allergen outgrown, age of diagnosis, age child outgrew allergy
Birth/Early Life	Mode of delivery, weeks of gestation at delivery, antibiotic use during pregnancy, Infections.
Comorbidities	Eczema, asthma, allergic rhinitis

FOUR CENTERS PRELIMINARY STUDY Findings

752 children with a diagnosis of IgE-mediated FA were recruited across 4 sites:

- **61.44%** males
- **35.9%** Non-Hispanic Black Children
- **54.26%** Non-Hispanic White Children
- **9.84%** Hispanic children

221(29.4%) out of 752 children outgrew at least 1 FA

- **36.27%** White children
- **22.22%** Black children
- **17.57%** Hispanic/Latinx children.

TABLE 1: Patient Characteristics		Outgrown At Least One FA (N=221)		No Outgrown FA (N=531)		Total (N=752)		P - Value
		N	% of Total	N	% of Total	N	% of Total	
Sex								0.834
	Female	87	30.00%	203	70.00%	290	38.56%	
	Male	134	29.00%	328	71.00%	462	61.44%	
Race/Ethnicity								<0.001*
	Hispanic	13	17.57%	61	82.43%	74	9.84%	
	NH Black	60	22.22%	210	77.78%	270	35.90%	
	NH White	148	36.27%	260	63.73%	408	54.26%	
Birth Country								0.0126
	USA	216	29.39%	519	70.61%	735	97.74%	
	Outside USA	3	100.00%	0	0.00%	3	0.40%	
	Unknown	2	14.29%	12	85.71%	14	1.86%	
Birth Type								0.9755
	Vaginal	140	29.23%	339	70.77%	479	63.70%	
	C-Section	76	29.80%	179	70.20%	255	33.91%	
	Unknown	5	27.78%	13	72.22%	18	2.39%	
Antibiotic During Pregnancy								0.0386
	Yes	24	20.87%	91	79.13%	115	15.29%	
	Unknown	197	30.93%	440	69.07%	637	84.71%	
Antibiotic During Birth								0.6425
	Yes	43	31.39%	94	68.61%	137	18.22%	
	Unknown	178	28.94%	437	71.06%	615	81.78%	
Household Annual Income								<0.001*
	Less than \$100,000	68	22.52%	234	77.48%	302	40.16%	
	\$100,000 - \$199,000	71	39.44%	109	60.56%	180	23.94%	
	More than \$199,000	60	32.26%	126	67.74%	186	24.73%	
	Declined to answer	19	28.36%	48	71.64%	67	8.91%	
	NA	3	17.65%	14	82.35%	17	2.26%	

FOUR CENTERS PRELIMINARY STUDY Findings

Race/ethnicity was significantly associated with report of having outgrown at least 1 food allergy (p<0.001).

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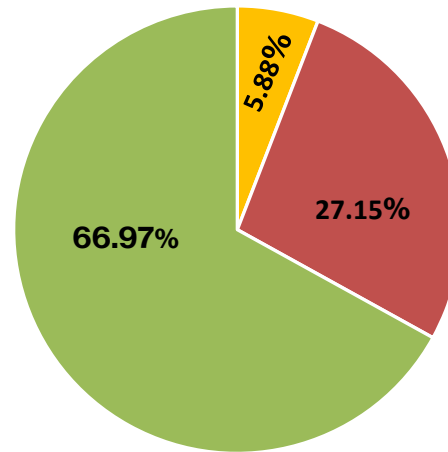
FOUR CENTERS PRELIMINARY STUDY Findings

Parents of Black and Hispanic children were less likely to report the development of food tolerance compared to White children.

Outgrown Food Allergies by Race/Ethnicity

Column Percentages

$P < 0.001$



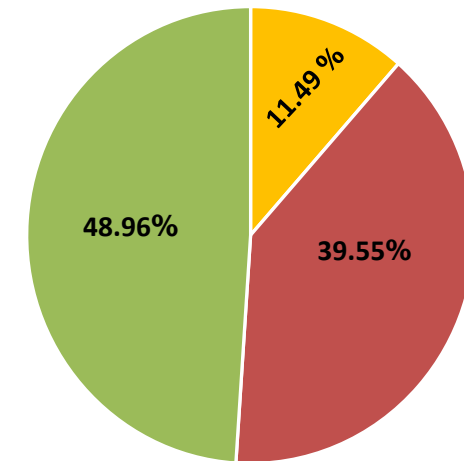
■ Hispanic ■ NH Black ■ NH White

In the OT group, 67% White children, 27% Black children and 6% Hispanic children developed food tolerance.

No Outgrown Food Allergies by Race/Ethnicity

Column Percentages

$P < 0.001$



■ Hispanic ■ NH Black ■ NH White

In the Active-FA group, 49% White children, 39.6% Black children and 11.5% Hispanic children did not outgrow any food allergy.

FOUR CENTERS PRELIMINARY STUDY Findings

- One of the main socioeconomic factors assessed in the intake survey was household income (<\$100,000, \$100,000 to \$199,000 and more than \$199,000).
- **Household income was significantly associated with outgrowing food allergy (p<0.001).**
- *OT group had 59.26% families earning >\$100,000 annually vs 44.5% families in the Active-FA group.*

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FOUR CENTERS PRELIMINARY STUDY Findings

No true statistically significant difference for gender, birth delivery methods, antibiotic use during pregnancy or at birth between the outgrown food allergy group and the active-FA group.

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FOUR CENTERS PRELIMINARY STUDY Findings

Early-onset or late-onset eczema was not associated with the development of food tolerance in this cohort.

Allergic rhinitis without other comorbid atopic conditions (p=0.0021) was associated with outgrowing FA, while asthma and eczema were not.

No statistically significant difference in the numbers of food allergies between the active-FA group and oral tolerance group.

TABLE 2.	Outgrown At Least One FA (N=221)		No Outgrown FA (N=531)		Total (N=752)		
Comorbidities	N	% of Total	N	% of Total	N	% of Total	P - Value
Asthma	101	29.71%	239	70.29%	340	45.21%	0.8215
Eczema	192	29.77%	453	70.23%	645	85.77%	0.4923
Allergic Rhinitis	145	33.72%	285	66.28%	430	57.18%	0.0021*
OAS	18	30.00%	42	70.00%	60	7.98%	1
Age of Diagnosis with Eczema							0.2205
0-6 months	122	32.02%	259	67.98%	381	50.66%	
7-12 months	33	33.00%	67	67.00%	100	13.30%	
above 12 months	27	23.89%	86	76.11%	113	15.03%	
NA	39	24.68%	119	75.32%	158	21.01%	
Food Allergies at Enrollment							0.2163
2 or less FA	70	26.42%	195	73.58%	265	35.24%	
More than 2 FA	151	31.01%	336	68.99%	487	64.76%	

FOUR CENTERS PRELIMINARY STUDY Findings

TAKE HOME POINTS:

White race, higher household income, and allergic rhinitis were associated with outgrowing food allergy.

We found caregiver-reported clinical tolerance/outgrown FA strongly associated with race and socioeconomic status suggesting that social determinants of health may be at play.

Limitations of this analysis:

- Cross-sectional
- Reported data are subject to recall bias.
- Sample size not equally represented. Underrepresentation of Hispanic children and absence of Asians participants.
- Crude Analysis; analysis did not adjust for any confounding factors.

FOUR CENTERS Preliminary ANALYSIS II

Caregiver-reported Data

- What are the types of food allergens outgrown?
- Does reaction history/severity influence the development of clinical tolerance?

FOUR CENTERS PRELIMINARY STUDY Methods

Data for this analysis came from all 4 centers.

We analyzed results of the intake survey completed by caregivers to investigate reaction history and the types of food allergens associated with the development of clinical tolerance.

Descriptive analysis was performed.

Logistic regression was used to investigate:

- The impact of caregiver-reported reaction history and severity on the probability of outgrowing food allergy.

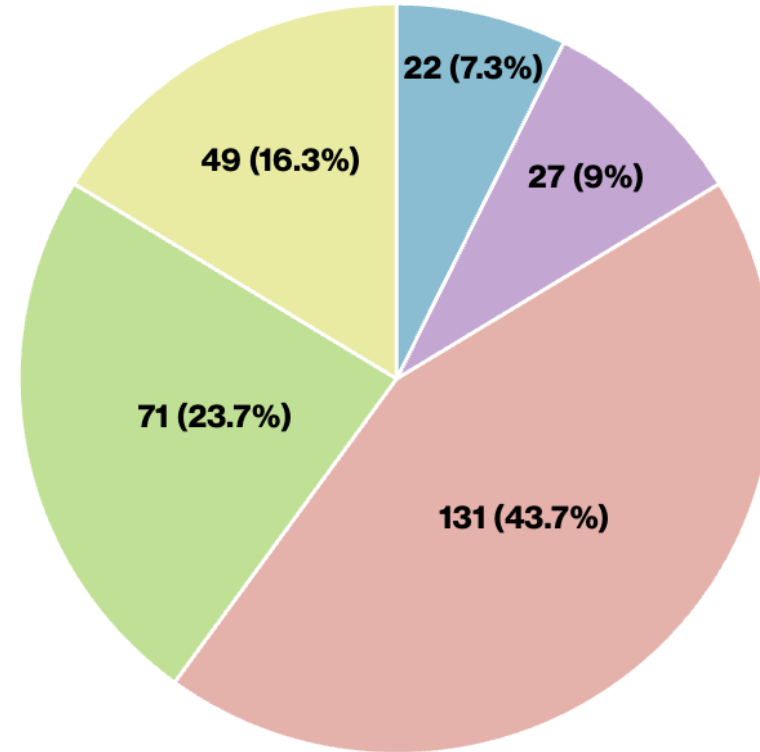
Analysis was adjusted for patient age, race, gender, institution, and comorbidities like asthma and eczema.

FOUR CENTERS PRELIMINARY STUDY Findings

Description	Count
Number of Patients	979
Number of Patients having outgrown ≥ 1 FA	247 (25% of total patients)
Total Number of reported outgrown FAs	663
<ul style="list-style-type: none">• Number of reported outgrown FAs <u>with history of reaction</u>	311 (47%)
<ul style="list-style-type: none">• Number of reported outgrown FAs <u>without history of reaction</u>	352 (53%)

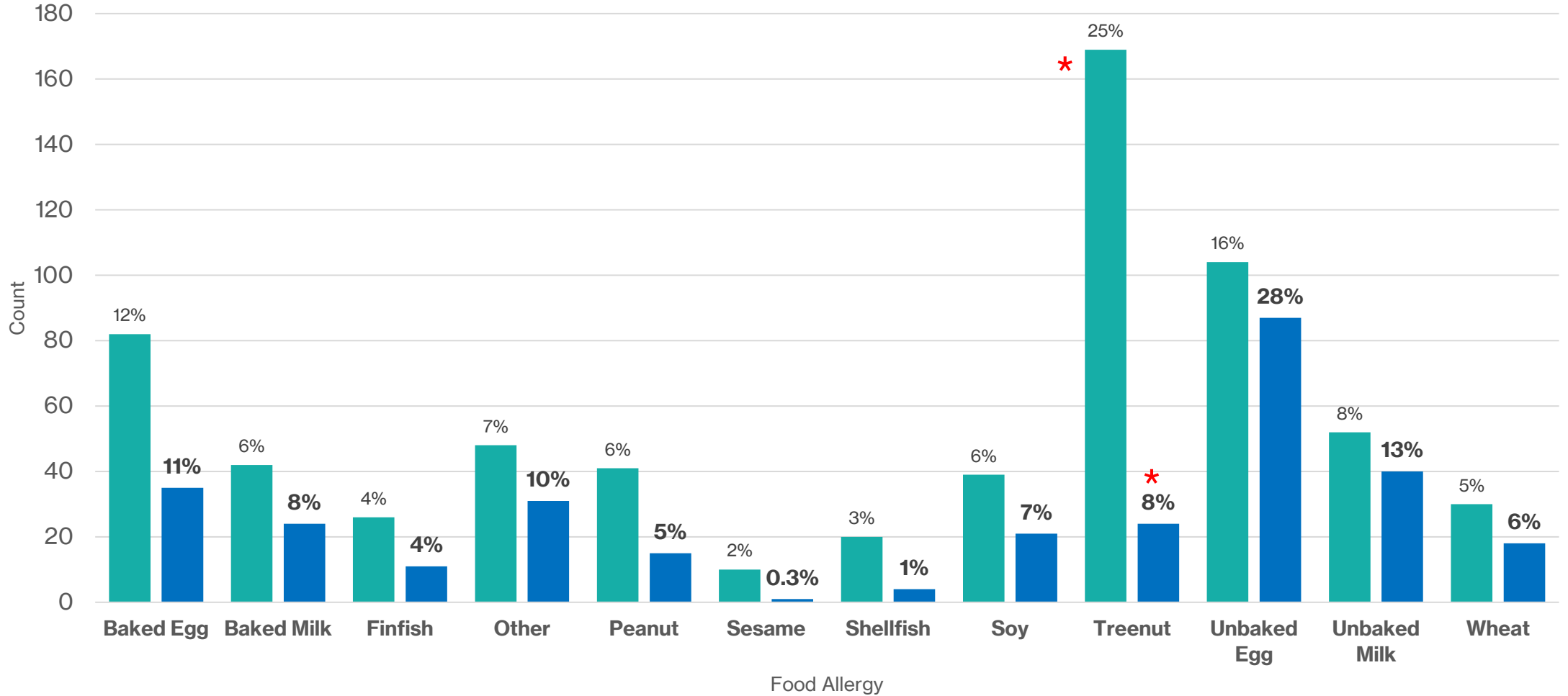
Outgrown Food Allergy Discovery in Children with a Reaction History

How food allergies were discovered to have been outgrown in children with a reaction history...



- Accidentally ate the food
- Ate food on purpose without health care provider's instruction
- Food Challenge under observation at health care provider's office
- Instructed by health care provider to do a food challenge at home
- Other

Number of Outgrown Food Allergies by Type



■ Number of Cases Regardless of Reaction History ■ Number of Cases With Reaction History

Egg → Milk → Treenuts → Soy → Wheat → peanut → Finfish → Shellfish → Sesame

FOUR CENTERS PRELIMINARY STUDY Findings

Table shows initial reactions for the 311 reported outgrown FAs with a reaction history.

Most of the reactions in the outgrown FA group involved 1-organ system (33.76%), followed by *2-organ systems (18%),* followed by more than 2-organ systems (13.50%) and 7% with a history of cardiovascular involvement.

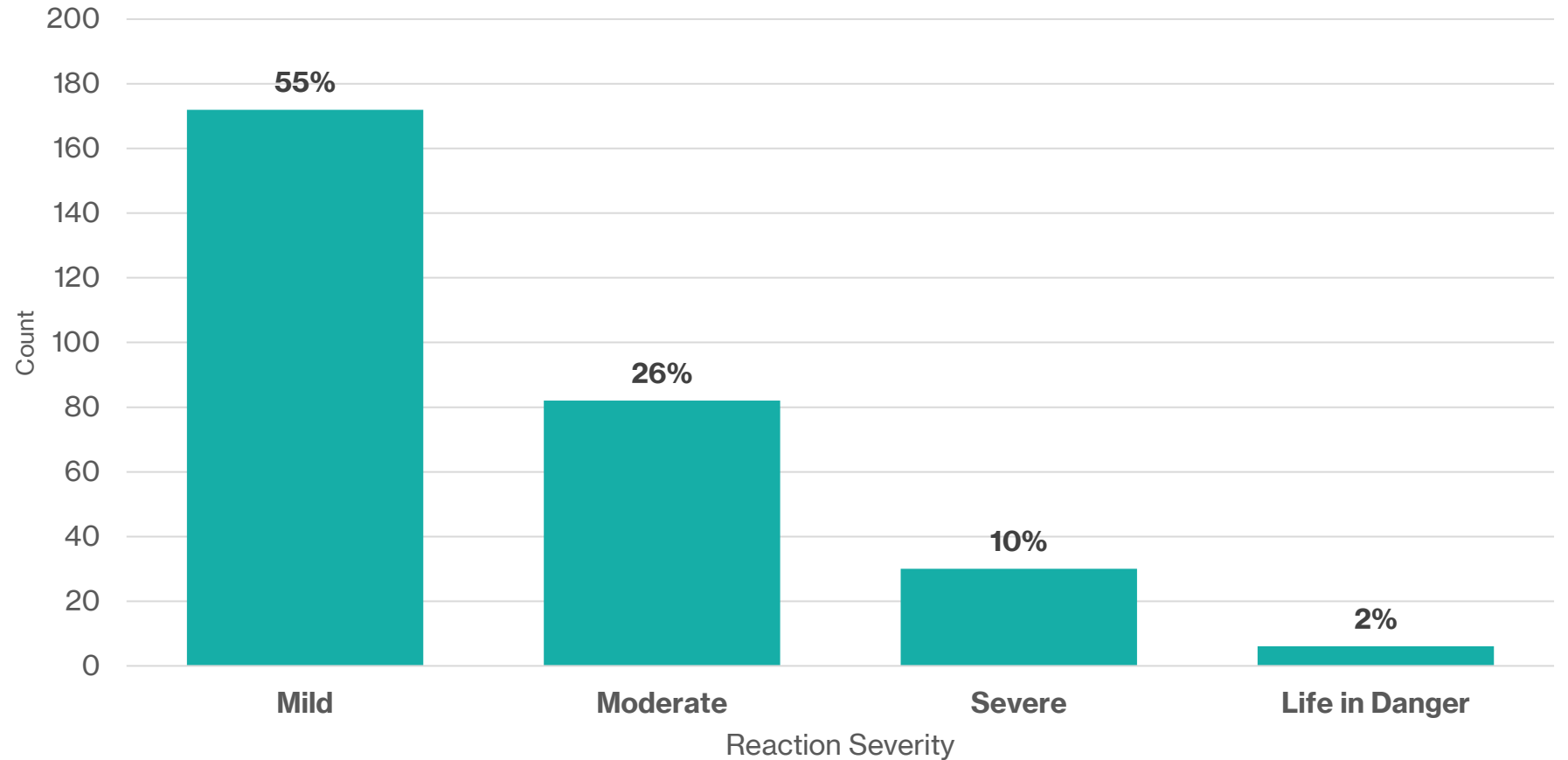
System Involvement	Initial Reaction
One Organ System:	105 (33.76%)
Skin	88 (28.30%)
GI	12 (3.85%)
Mouth	4 (1.29%)
Other	1 (0.32%)
2 Organs Systems:	56 (18%)
Skin + GI	26 (8.36%)
Skin + Mouth	11 (3.55%)
Skin + Breathing	8 (2.57 %)
Skin + Other	5 (1.60%)
Mouth + GI	2 (0.64%)
Breathing + GI	2 (0.64%)
Mouth + Breathing	1 (0.32%)
Other+ Mouth	1 (0.32%)
More than 2 Organs Systems (No cardio)	42 (13.50%)
Cardio (regardless of other reactions)	7 (2.25%)
N/A	101 (32.48%)

FOUR CENTERS PRELIMINARY STUDY Findings

Mild reactions were better predictors of outgrowing FA. Most the reported outgrown FA had a history of mild reaction.

However, based on the caregiver-reported data, some children with a history of severe reaction were also able to develop clinical tolerance.

Number of Specific FAs Outgrown by Caregiver Reported Reaction Severity



The probability of outgrowing a food allergy diminishes with increasing severity of the initial reaction.

- **Moderate severity reactions** were associated with a **65% lower chance of outgrowing food allergies** compared to mild reactions.
- **Severe reactions** were associated with an **87% reduction in the likelihood of developing clinical tolerance**.
- The odds of outgrowing food allergies in cases of **highest reaction severity**, were associated with a **94% reduction in the likelihood of outgrowing food allergies** compared to mild reactions.

Dependent Variable: Ever Outgrown a Food Allergy			
Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	P-Value
Reaction Severity (Base is mild)			
• Moderate	0.35	0.27 – 0.45	< 0.001
• Severe	0.13	0.10 – 0.18	< 0.001
• Life in Danger	0.06	0.02 – 0.22	< 0.001

FOUR CENTERS PRELIMINARY STUDY Findings

TAKE HOME POINTS:

- Food Allergies can be outgrown. Like other studies, egg and milk were the most outgrown FA, possibly suggesting that the likelihood of outgrowing FA is associated with the type of food allergen.
- **Based on this analysis, mild reactions were better predictors of outgrowing FA, however severe reactions do not completely preclude the development of tolerance.**
- **The significant difference in tree nut allergy cases between those with a reaction history (8%) and those without a reaction history (25%) suggests that panel testing may influence caregiver perceptions of tree nut allergies.**

Limitations of the study:

- Cross-sectional
- Reported data are subject to recall bias.

Conclusions

- **Currently, we do not clearly understand why some children outgrow their food allergies and others do not. More research is needed to help improve our understanding of food allergy and the development of clinical tolerance.**
- We observed that there are racial, ethnic, and socioeconomic differences in the development of clinical tolerance in food allergy.
- We observed that children with private insurance were more likely to outgrow their food allergies than those with Medicaid/public insurance.
- We observed that children from homes with higher household income were more likely to report outgrowing food allergies.
- **Social determinants of health are most likely playing a role. It is thus important to consider how social determinants of health can influence outcomes in children with food allergies in clinical practice.**

Conclusions

- **We observed that food allergies can be outgrown and that some food allergies may be more likely to be outgrown than others.**
- We observed that allergic rhinitis without other comorbid atopic conditions was associated with outgrowing FA, while asthma and early- or late onset eczema were not.
- **We observed that reaction severity influenced the likelihood of outgrowing a food allergy.**
- We observed caregivers reporting allergies to some foods without any history of prior reactions to those foods; then later reporting those foods as outgrown FA. This raises questions about the possible impact of panel testing on caregiver perceptions and behavior. Food allergy panel testing can result in misdiagnosis or overdiagnosis and negatively impact the nutritional status of children, leading to a restricted diet. Patient/caregiver education and understanding are thus crucial.
- **We are currently working on refining the data and on more comprehensive analyses to not only confirm the findings shared in this presentation, but to further identify and understand predictors associated with the development of clinical tolerance in children with food allergy.**



Questions?