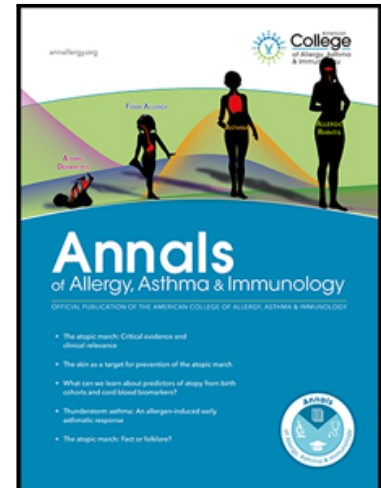


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Differences in oral food challenge reaction severity based on increasing age in a pediatric population

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Title: Differences in oral food challenge reaction severity based on increasing age in a pediatric population

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Katie Kennedy MD: Lead author of this paper, collected data, wrote/edited several drafts of entire manuscript

Maria K.C. Alfaro: Participated in data extraction and entire data analysis, figure design, wrote/edited several drafts of entire manuscript

Zachary C. Spergel: Participated in data extraction and entire data analysis, figure design, wrote/edited several drafts of entire manuscript

Stacy L. Dorris: Participated in data extraction, wrote/edited several drafts of entire manuscript

Jonathan M. Spergel: Participated in data extraction and entire data analysis, figure design, wrote/edited several drafts of entire manuscript

Peter Capucilli: Senior author of this paper, collected data, wrote/edited several drafts of entire manuscript

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Abbreviations

FA: Food Allergy; OFC: Oral Food Challenge; EMR: Electronic medical record; IgE: Immunoglobulin E; CV: Cardiovascular; N: Neurologic; LR: Lower respiratory; L: Laryngeal

ED: Emergency department, SPT: skin prick test

Background : Food allergy (FA) reactions range from mild to severe with differences in age appearing to be an important factor associated with reaction severity.

Objective : To define differences in oral food challenge (OFC) reaction severity in pediatric patients from infancy to adolescence using objective clinical outcomes and standardized reaction grading tools.

Methods : Retrospective review of all positive OFCs at two large institutions between September 2016 and February 2019. Reaction severity was defined by presence of cardiovascular, neurologic, lower respiratory or laryngeal symptoms (CV/N/LR/L), epinephrine requirement and grading using two established FA reaction scales. **Results :** Infants and toddlers demonstrated fewer reactions involving CV/N/LR/L symptoms compared to older age groups. Epinephrine was also required less frequently during reactions in infants and toddlers, compared to older age groups. There was no difference in reaction severity in infants and toddlers based on clinical history of eczema. Increasing age was significantly correlated with increased epinephrine requirement ($R^2 = 0.12$, $p = 0.002$), elevated CoFAR score ($R^2 = 0.012$, $p = .003$), and approached significance for increased PRACTALL score ($R^2 = 0.005$, $p = .057$). History of asthma and sesame allergy were identified to be positively correlated with more severe reactions.

Conclusion : Infants and young toddlers demonstrate less severe reactions during OFCs compared to older age groups supporting early food introduction practices. In children under 12 months of age, severe reactions are most rare calling into question screening practices using specific allergy testing prior to food introduction. Standardized reaction grading tools may be valuable instruments to categorize reaction severity during OFCs.

Introduction

IgE-mediated food allergy (FA) reactions in infants, children, and adolescents differ in severity, ranging from mild to severe, and in rare cases, life threatening.^{1,2} Both the definition of a “severe” allergic reaction, however, and the factors underlying differences in reaction manifestation remain an area of active research, with our collective robust understanding of this topic likely incomplete.^{1,3-5} Recent estimates of FA prevalence rates in children have dramatically increased over the past three decades, currently ranging between 8-10% globally, and effectively impacting roughly 1 in 13 children.^{6,7} Given this, prevention of food allergy development through early food introduction has rapidly become one of the most important practices in our field of late, largely owed to the findings of the Learning Early About Peanut (LEAP) and the Enquiring About Tolerance (EAT) trials, amongst several other high-quality research efforts.⁸⁻¹⁰

Screening infants or young children using allergen-specific tests, including skin prick tests (SPTs) and serum immunoglobulin E (IgE) tests prior to food ingestion has been controversial in clinical practice. While testing prior to ingestion may circumvent an initial reaction in allergic children, the accuracy of these tests (without prior high pre-test probability) is weak.¹¹⁻¹⁵ The intrinsic low positive predictive value, low specificity and resultant high false positive rates associated with testing can result in unnecessary food avoidance and mislabeling patients as food allergic in those who might be clinically tolerant. This is especially important to consider given the continued use of multiple food IgE panels, especially amongst non-allergist providers.¹⁶

A recent consensus report for the prevention of FA suggests that allergenic foods, including peanut and egg, should be introduced around 6 months of age.¹⁷ While FA screening before introduction is not recommended, parental preference or expectation for testing prior to ingestion was acknowledged. This is especially clinically palpable for the practicing clinician, for instance, in situations in siblings with FA or in the setting of severe atopic dermatitis.^{18,19, 8,17}

In 2019, The EarlyNuts study evaluated a non-screening approach to early peanut introduction in both low and high-risk infants under 12 months of age.²⁰ While a 4.0% reaction rate was reported, the vast majority of reactions involved isolated cutaneous symptoms with only 0.3% of those introduced to peanut demonstrating reactions involving wheezing. Although a higher overall reaction rate was noted compared to the former HealthNuts study, the authors found no difference in proportion of reactions

associated with wheezing between the two studies, despite screening for high-risk infants in HealthNuts.²¹ These data call into question the necessity of any FA screening before food ingestion in infants whatsoever, despite risk level. Similar studies associated with early food introduction have also demonstrated mild reactions in those that were elicited, with very few, if any, reactions in young infants involving cardiovascular, neurologic or respiratory symptoms.^{8,22-24}

In consideration of reaction severity, several objective grading scales have been utilized in both the clinical and research settings for reaction characterization, however, few studies have utilized these scales within the infant population or with large scale physician-observed oral food challenge (OFC) outcomes data.^{1,25,26} Thus, we sought to evaluate differences in reaction severity during OFC, using established objective grading scales, within a large pediatric cohort. We hypothesized that age, as an independent risk factor, may account for differences in reaction severity amongst food allergic individuals from infancy to adolescence.

Methods

Protocol and data extraction

We performed a retrospective chart review of all OFCs at the Children's Hospital of Philadelphia (CHOP), Philadelphia, Pennsylvania and Vanderbilt University Medical Center (VUMC), Nashville, Tennessee between 9/9/16 to 2/28/19. All OFCs were open, direct physician-observed and performed using protocols based on well-established OFC practice guidelines, as formerly outlined by Capucilli et al. and others.^{27,28,29} None of the challenges reviewed were conducted in double blinded fashion. All patients were referred to undergo OFC for clinical purposes. All research-specific OFC outcomes were excluded. At CHOP, OFCs were conducted in a hospital-based unit. Challenges at VUMC were performed in the outpatient allergy clinic. OFCs eliciting a positive reaction at CHOP were graded using the PRACTALL score and were entered into the electronic medical record (EMR) by a dedicated allergy nurse at the time of challenge.²⁹ All challenges at VUMC were retrospectively graded using the PRACTALL score by an attending allergist (S.L.D). Reactions at both institutions were also retrospectively scored using the CoFAR Anaphylaxis Severity Score²⁵ based on review by 2 attending allergists and with discrepancies differences by a third allergist (K.K, P.C., J.M.S, S.L.D).

Using each institution's EMR (Epic Systems, Verona, Wisconsin), we elicited relevant patient clinical data, including, age, gender, atopic history (asthma, allergic rhino-conjunctivitis, atopic dermatitis) and specific patient food allergies as documented within the primary allergist's clinic note and as extracted from the EMR "Allergy" tab. Additionally, required treatment during OFC reaction, including use of epinephrine was obtained. The study was approved by each individual site's institutional review board.

Classification of severity

We categorized reaction severity based on several parameters. Patients were initially divided by 5 general age group categorizations including, 0-1 years (infants), 1-2 years (toddlers), 3-5 years (young children), 6-12 years (older children), 13-18 years (adolescents). Groupings were adapted from previous standardized reports for pediatric trials.³⁰ As formerly described by our group, we assessed differences in reaction severity based on presence or absence of specific reaction symptoms including, cardiovascular, neurologic, lower respiratory or laryngeal (CV/N/LR/L) findings, as these symptoms have been consistently graded amongst the highest severity categories across various scales.^{25,26,29} Differences in epinephrine requirement based on age categorization were also assessed. Using these measures of severity, we further delineated severity differences in OFC outcomes in infants and toddlers based on the presence or absence of atopic dermatitis (eczema) diagnosis. We next performed a regression analysis of age to correlate severity of OFC reaction based on two objective reaction grading scales. For this, we chose the PRACTALL scale and CoFAR Anaphylaxis Severity Score based on both our clinical experience with these scales as well as use in clinical trials data.^{25,29} Linear age was also assessed for statistical correlation with epinephrine requirement. Finally, we sought to assess the impact of multiple variables on severity outcomes based on the PRACTALL and CoFAR scales as well as epinephrine requirement.

Statistical Analysis

Prevalence rates for baseline patient characteristics, including age (median and range values), gender, atopic histories (history of allergic rhinitis, asthma, atopic dermatitis, urticaria), specific food challenged and epinephrine requirement were compiled for each individual institution. The χ^2 analysis of independent variables was used to compare differences in reaction severity based on specific clinical reaction symptoms (CV/N/LR/L) as well as differences in epinephrine requirement between age groups. For these analyses, infants and toddlers were combined given wider range of ages in older age groupings. Next, a linear regression analysis of age compared to reaction severity defined by PRACTALL and CoFAR scores and epinephrine requirement was performed. Finally, we completed a multivariable analysis of all elicited factors as independent variables, including (age, gender, atopic histories and food challenged), to determine the impact of these factors on PRACTALL and CoFAR scores, as well as epinephrine requirement. For all outcomes, a *P* value less than 0.05 was considered statistically significant. Data were analyzed using GraphPad v.8 (Prism Software, San Diego, California) and Stata v.15 (College Station, Texas).

Results

Demographics and overall outcomes

A total of 746 OFC reactions from both institutions were reviewed involving 675 unique patients as outlined in Table 1. The median age of the total cohort was 6 years (0.5-18.7 years) with 32% of the cohort being female. Amongst atopic histories, history of atopic dermatitis (eczema) and asthma were most common, 59% and 58%, respectively. Peanut was the most frequently challenged food involving reaction (26%) for all ages. Specific food reaction for each age group were enumerated and included as an eSupplement (eTable1). Between CHOP and VUMC, a total of 19% reactions involved CV/N/LR/L

symptoms and 59% of reactions required epinephrine. Median overall PRACTALL and CoFAR scores were 4 (range = 1-24) and 2 (range = 1-5), respectively.

Differences in symptoms and epinephrine requirement based on age groups

There was an age-dependent significant difference in the number of CV/N/LR/L reactions based on age categorizations. Infants and toddlers had significantly fewer reactions involving CV/N/LR/L symptoms compared to older age groups (10% vs 22%, $p=0.0013$) with 88% of these reactions occurring in young children, older children and adolescents. No statistical difference in CV/N/LR/L symptom occurrence was appreciated between infants and toddlers, however, only 1 infant met clinical criteria for a CV/N/LR/L reaction, with a reaction involving wheezing. Comparing individual age groups, infants and toddlers had significantly fewer overall reactions involving CV/N/LR/L symptoms (10%) compared to children (23% in young children, $p=0.002$ and 22% in older children, $p=0.003$) and approached significantly fewer CV/N/LR/L reactions compared to adolescents (19%, $p=0.08$). (Figure 1A). Considering infants individually, fewer CV/N/LR/L reactions were noted (3%) compared to older age groups ($p=0.008$ vs young children; $p=0.02$ vs older children; $p=0.04$ vs adolescents) (not graphically shown). Similarly, epinephrine requirement was lower in composite infants and toddlers (47%) compared to young children (61%, $p=0.007$), older children (62%, $p=0.002$) and adolescents (67%, $p=0.003$) (Figure 1B).

In the youngest two age groups (infants and toddlers), we found no significant difference in OFC reactions involving CV/N/LR/L symptoms or reactions requiring epinephrine in individuals with or without diagnosis of atopic dermatitis ($p=0.60$ and $p=0.68$, respectively) (Figure 2AB).

Differences in reaction grading and epinephrine based on linear age

In the simple regression model, there was a significant correlation between increasing age and total CoFAR score ($R^2=.012$, $p=.003$) and between increasing age and epinephrine requirement ($R^2=.012$, $p=.002$). In assessment of total PRACTALL score, there was a notable trend approaching significance between increasing age and increase in total PRACTALL score ($R^2=.005$, $p=.057$). In the regression model including multiple variables, asthma was retained as a significant predictor of both a higher total CoFAR ($p=0.005$) and PRACTALL ($p=0.019$) score, approaching but not reaching significance in predicting a significantly higher epinephrine requirement ($p=0.076$). Similarly, sesame challenges were associated with significantly higher total CoFAR ($p=0.014$) and total PRACTALL scores ($p=0.001$), as well as increased epinephrine requirement ($p=0.034$).

Discussion

In this study, we defined differences in severity of OFC reactions across the spectrum of pediatric ages from infancy to adolescence. Using presence of CV/N/LR/L symptoms and epinephrine requirement at time of reaction as markers severity, we found that infants and toddlers, in general, tend to have significantly less severe reactions compared to children in older age groups. Severe reactions involving the above critical body systems were particularly rare in the infant age group (<1 year of age),

where only 1 patient (accounting for 3% of reactions) experienced a reaction involving wheezing (LR). Of note, in our data set, we had zero infants who experienced any cardiovascular or neurologic symptoms as well as zero infants who experienced a reaction involving stridor that could be suggestive of airway obstruction.

These data have important implications regarding the safety of allergenic food introduction in infants. The vast majority of those infants who underwent OFC and reacted to the challenged food experienced reactions that were mild in nature, only rarely involving more objectively severe symptoms and treatment requirement. Our data may also support the timely performance of OFCs to definitively determine allergy status. This is particularly important in several clinical scenarios, including infants with positive SPT or serum IgE tests with no history of food ingestion, as well as patients with indeterminant reaction history or specific allergy test results. While the overall decision to perform an OFC should weigh in parental preference, the above data can be utilized as a reassuring point in discussion with families regarding the risks and benefits associated with performing an OFC.

Our study is not the first to assess age differences in severity of FA reactions. Of note, there currently exists no reports of infant mortality associated with food introduction below the age of 2 years.² Data ranging from parental surveys to emergency department (ED) analyses have also found that infants overall tend to have less severe reactions compared to older children.^{31, 32} In one large cohort study, infants (<1 years old) presenting to the ED with anaphylaxis experienced fewer respiratory symptoms compared to older children (2-4 years of age), directly correlative with our findings.³² Also consistent with our study are reports of more frequent respiratory symptoms in infants 12-23 months old as compared to those under 12 months of age.³³ This suggests that there may be a definite increase in potential reaction severity in children after the first year of life, which is undoubtedly an important finding that requires further investigation.

Given the association of severe atopic dermatitis and previous egg allergy as risk factors for peanut anaphylaxis, as utilized in the LEAP trial, we further sought to explore this within our cohort as recent investigations have brought into question the impact of these concerns on multiallergen testing and increased diagnosis.³⁴ Unfortunately, due to the limitations of our retrospective review, we were unable to delineate which infants/toddlers had been diagnosed previously with an egg allergy or classified as having severe atopic dermatitis, however, we used a global baseline diagnosis of atopic dermatitis as a surrogate marker for this cohort in our youngest age groups. We found no significant difference in clinical reaction severity or epinephrine requirement in those with or without atopic dermatitis, suggesting that targeted screening prior to food introduction, even in this “high risk” population is likely unnecessary.

One clinical factor that was noted to be significantly associated with a more severe food reaction in our data set was history of asthma, which has consistently been reported as a risk factor for severe anaphylaxis as well as fatal anaphylaxis.^{4, 35} Additionally, we found that sesame allergy was retained as a risk factor for a severe allergic reaction upon challenge to sesame within our multivariate analysis, which is an important clinical consideration, especially as sesame allergy prevalence has increased in the United States³⁶. This also supports federal law mandating declaration of sesame on food labeling.

While our data most significantly supports previous efforts describing differences in reaction severity based on age, our findings uniquely demonstrate these differences using a large cohort of patients during physician-observed OFCs, and utilizing objective reaction grading tools, the PRACTALL and CoFAR scores. Our findings demonstrate that both tools may be valuable for clinicians in the effort to standardize OFC reaction descriptions and classification of severity. We have previously shown that correlation between these scales are overall poor,¹ however, it is our opinion that a definite standardized approach to grading food challenge reactions may be important in discriminating which children experience severe compared to non-severe reactions, especially from a translational research perspective.

The primary limitation of our study is in the retrospective nature of our data analysis. While all patients were referred for clinical purposes (and not for research OFCs), the underlying reasons to pursue challenge were not able to be obtained through retrospective review and could bias our outcomes. For example, patients with positive testing but without clinical reaction referred for OFC to facilitate introduction may have experienced less severe reactions compared to patients undergoing challenge to assess for outgrowth of an established allergy (especially if the clinical reaction was too severe to warrant OFC at a younger age). Further, our data are comprised of OFC outcomes from two pediatric academic centers with large referral bases, which may introduce selection bias with potentially severely allergic patients who have been referred to a tertiary care center. There is also some inconsistency between the two institutions included in the study in terms of reaction grading. Whereas PRACTALL scores were graded in real time during OFC at CHOP, PRACTALL scores (as well as CoFAR scores for both institutions) were retrospectively graded at VUMC and thus may be limited due to reaction interpretation based on physician chart review. OFC data presents intrinsic limitations and strengths as well. We certainly acknowledge that patients who were thought to be definitively allergic to a food upon evaluation were most likely not referred for OFC and so assessment of severity of reaction in these patients cannot be extrapolated from our data. Treatment decisions during OFCs can also be difficult to standardize, regardless of reaction classification. We acknowledge here the higher percentage of young patients who received epinephrine compared to those meeting our clinical criteria for severity. At both institutions, OFCs are conducted by multiple providers and so the decision to administer specific therapies, including epinephrine, is subject to provider discretion. Thus, our data may under or overestimate the primary outcome of epinephrine delivery during reaction. Additionally, in the OFC setting, treatments may be administered more rapidly compared to the real-world situation, which may impact overall reaction outcome. In contrast, quantification of directly observed objective symptoms is a strength of these data. Finally, we acknowledge that the definitions of “severity” as we have defined within this study are not standardized across the spectrum of research and clinical practice. We chose to delineate CV/N/LR/L symptoms, for instance, as severe based on our clinical consensus and based on review of previously utilized grading tools.

In summary, we demonstrate significant differences in OFC reaction severity based on patient age with an increasing propensity for more severe reactions in older age groups. Consistent with numerous previous efforts³⁷ our data demonstrate that infants rarely suffer severe allergic reactions and require less epinephrine to treat these reactions compared to older children. Therefore, we argue for

early allergenic food introduction, and use of standardized reaction grading scales to objectively quantify OFC outcomes. Further research is necessary to determine the overall safety of open food introduction in all infants (regardless of risk) without first performing specific allergy testing. Similarly, correlation between eliciting doses and severity of reactions would also provide important information in regards to food introductions. Still, these results should empower both physicians and families to introduce allergenic foods to infants early, if deemed to be lower risk, with the knowledge that a severe reaction is unlikely to occur.

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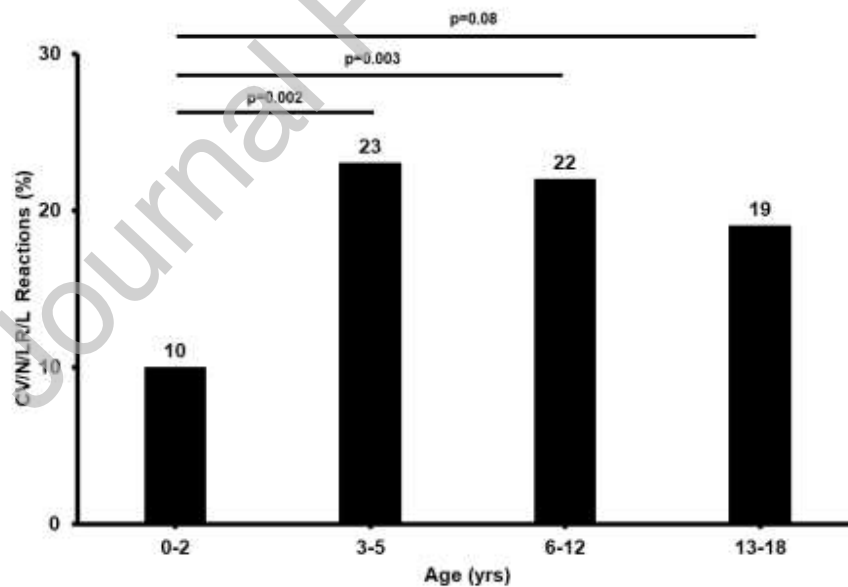
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Figure Legends:

Figure 1. A. Percent differences in oral food challenge reactions involving cardiovascular, neurologic, lower respiratory or laryngeal symptoms based on age groupings. B. Percent difference in epinephrine requirement during oral food challenge reactions based on age groupings. Abbreviations: CV/N/LR/L, cardiovascular, neurologic, lower respiratory, laryngeal.

Figure 2. Percent difference in A. severe clinical reactions and B. reactions requiring epinephrine based on presence or absence of atopic dermatitis (AD) in Infants and Toddlers (0-2 years) for all foods. Abbreviations: CV/N/LR/L, cardiovascular, neurologic, lower respiratory, laryngeal.

Figure 1**A.**

B.

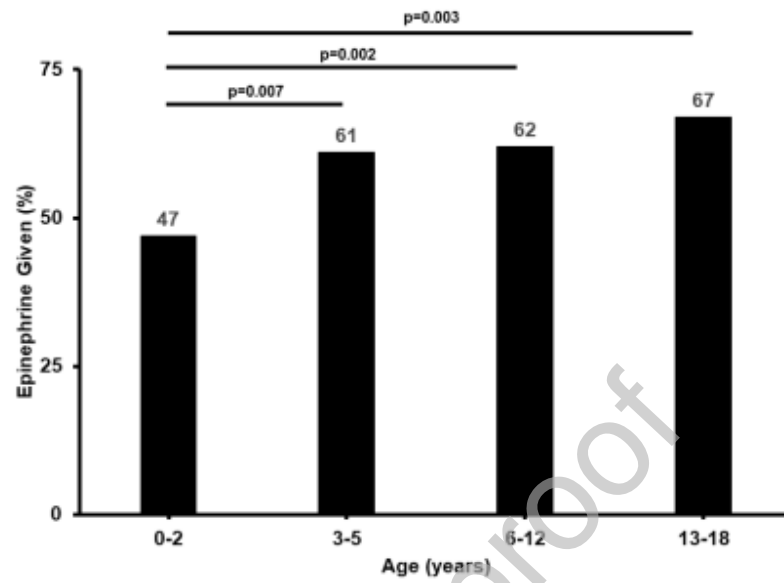
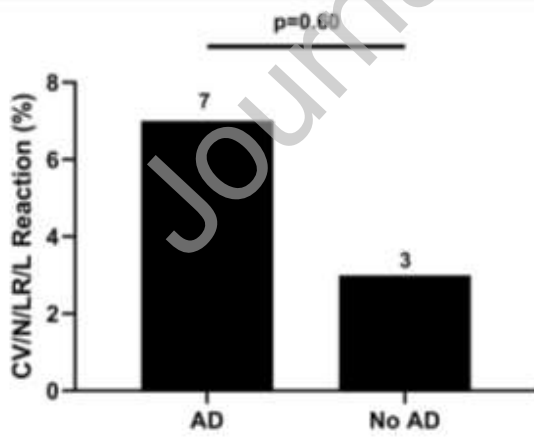
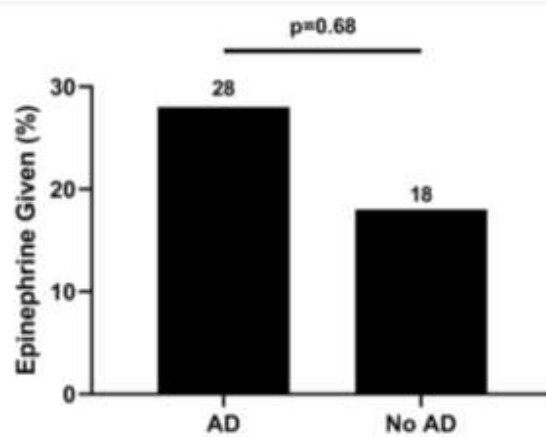


Figure 2

A.



B.



Tables:**Table 1** – Demographics and Reaction Outcomes

	CHOP	VUMC	Overall
Total Reactions (n, %)	679 (91%)	67 (9%)	746
Gender (n, %)			
Female	213 (29%)	25 (3%)	238 (32%)
Male	466 (62%)	42 (6%)	508 (68%)
Overall Age (Median, Range)	6, 0.6-18.7	3, 0.5-18	6, 0.5-18.7
Age Grouping (n, %)			
Infants (0-1 years)	22 (3%)	9 (1%)	31 (4%)
Toddlers (1-2 years)	109 (15%)	23 (3%)	132 (18%)
Young Children (3-5 years)	200 (27%)	12 (2%)	212 (28%)
Older Children (6-12 years)	272 (37%)	14 (2%)	286 (38%)
Adolescents (13-18 years)	76 (10%)	9 (1%)	85 (11%)
Atopic History (n, %)			
Asthma	419 (62%)	15 (22%)	434 (58%)
Allergic Rhinoconjunctivitis	255 (38%)	26 (39%)	281 (38%)
Atopic Dermatitis	395 (58%)	44 (66%)	439 (59%)
Food Challenged (n,%)			
Peanut	168 (23%)	29 (4%)	197 (26%)
Egg	147 (20%)	3 (0.4%)	150 (20%)
Baked Egg	94 (13%)	10 (1%)	104 (14%)
Milk	63 (8%)	3 (0.4%)	66 (9%)
Baked Milk	24 (3%)	1 (0.1%)	25 (3%)
Wheat	23 (3%)	1 (0.1%)	24 (3%)
Sesame	18 (2%)	0 (0%)	18 (2%)
Soy	10 (1%)	4 (0.5%)	14 (2%)
Tree Nuts*	106 (14%)	13 (2%)	119 (16%)
Fish/Shellfish**	15 (2%)	1 (0.1%)	16 (2%)

Other ***	11 (2%)	2 (0.3%)	13 (2%)
Total CV/N, LR/L (n, %)	131 (18%)	12 (2%)	143 (19%)
Total Epinephrine (n, %)	419 (56%)	21 (3%)	440 (59%)
Total PRACTALL score (Median, Range)	5, 1-24	3, 1-10	4, 1-24
Total CoFAR score (Median, Range)	2, 1-4	1, 1-4	2, 1-4

* Tree Nuts = walnut, pecan, cashew, hazelnut, almond, pistachio, brazil nut

** Fish/Shellfish = salmon, shrimp, cod, calamari, crab, lobster

*** Other = barley, black bean, chicken, chickpea, coconut, lentil, mustard, peas, pork, pumpkin, sunflower seed

Total CV/N/LR/L = total number at each site involving either cardiovascular, neuro, lower respiratory or laryngeal reaction

Total Epinephrine = total number of reactions requiring epinephrine.

Table 2 – Regression analyses of age vs total PRACTALL score, CoFAR score, epinephrine administration

Dependent Variable	Regression	Variable	R squared	P
PRACTALL	Simple	Age	0.005	0.057
	Multiple	Asthma	-	0.019
	Multiple	Sesame	-	0.001
CoFAR Score	Simple	Age	0.012	0.003
	Multiple	Asthma	-	0.005
	Multiple	Sesame	-	0.014
Epinephrine	Simple	Age	0.012	0.002
	Multiple	Asthma	-	0.076
	Multiple	Sesame	-	0.034

eTable 1 – Specific food reactions delineated by age groupings

Food Challenges (N=746)	Infant 31(4%)	Toddlers, 132 (18%)	Young Children, 212 (28%)	Older Children, 286 (38%)	Adolescents, 85 (11%)
Peanut	17 (55%)	38 (29%)	46 (22%)	75 (26%)	21 (25%)
Egg	7 (23%)	42 (32%)	40 (19%)	51 (18%)	10 (12%)
Baked Egg	2 (6%)	18 (14%)	45 (21%)	33 (12%)	6 (7%)
Milk	4 (13%)	15 (11%)	19 (9%)	20 (7%)	8 (9%)
Baked Milk	0 (0%)	1 (1%)	5 (2%)	15 (5%)	4 (5%)
Wheat	0 (0%)	4 (3%)	11 (5%)	8 (3%)	1 (1%)
Sesame	0 (0%)	3 (2%)	6 (3%)	7 (2%)	2 (2%)
Soy	1 (3%)	2 (2%)	2 (1%)	6 (2%)	3 (4%)
Tree Nuts*	0 (0%)	5 (4%)	33 (16%)	58 (20%)	23 (27%)
Fish/Shellfish**	0 (0%)	2 (2%)	2 (1%)	9 (3%)	3 (4%)
Other***	0 (0%)	2 (2%)	3 (1%)	4 (1%)	4 (5%)

* Tree Nuts = walnut, pecan, cashew, hazelnut, almond, pistachio, brazil nut

** Fish/Shellfish = salmon, shrimp, cod, calamari, crab, lobster

*** Other = barley, black bean, chicken, chickpea, coconut, lentil, mustard, peas, pork, pumpkin, sunflower seed

Column percentages are based on age groupings