

Relationship between treatment with antacid medication and the prevalence of food allergy in children

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ABSTRACT

Food allergy affects 8% of preschool children, but factors responsible for food allergy in children are poorly understood. Use of antacid medication may be a contributing factor. The purpose of this study was to determine if parent-reported antacid medication use was associated with higher prevalence of food allergy in atopic children. In this cross-sectional study, parents of children with atopic diseases completed a questionnaire relating to a history of treatment with antacid medication and food allergy. Charts were independently reviewed for food-specific IgE and/or skin-prick test results. Food allergy was defined as a reaction to a food consistent with the anaphylaxis consensus statement and either an elevated food-specific IgE or a positive food skin-prick test. One hundred four questionnaires were completed. Mean age of the participating children was 7.0 ± 4.3 years (range, 5 months to 18 years of age). Forty-seven (45%) individuals were reported to have taken an antacid medication in the past. History of taking antacid medication was associated with an increased prevalence (57% ^{27/47} versus 32% ^{18/57}) and higher prevalence of food allergy of having food allergy (aPR, 1.7 [1.1–2.5]). Mean peanut food-specific IgE was higher in those with a history of taking antacid medication (11.0 ± 5.0 versus 2.0 ± 5.5 ; $p = 0.01$). History of treatment with antacid medication is associated with an increased prevalence of having food allergy.

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Food allergy is estimated to affect 8% of children ≤ 4 years old.^{1–3} It is the most common cause of anaphylaxis in children presenting to the emergency room, with ~150 deaths reported in the United States caused by food allergy each year.⁴ The prevalence of food allergy has increased 18% in the United States since 1997.⁵ The reasons for the increase in prevalence are poorly defined.

Although some risk factors have been proposed (antacid medication, delay in introduction of foods, etc.), definitive evidence linking these risk factors to the development of food allergy is lacking especially in children.

Gastroesophageal reflux (GER) is also very common in this same age group (infants and young children) and affects 10–30% of that population.^{6,7} Treatment of GER includes use of antacid medications (proton pump inhibitors [PPIs] and H₂-blockers), which reduce the amount of hydrochloric acid produced by the parietal cells in the stomach thereby increasing gastric pH.

There is some evidence linking treatment with antacid medications to development of food allergy in humans. Use of antacid medication is known to increase sensitization to food (either skin-prick testing or food-specific IgE) in adults.⁸ Milk allergy appears to be prevalent (33%) in children diagnosed with GER disease.⁹ Development of food allergy to hazelnut has been associated with antacid therapy in both murine models and human adults.¹⁰ In murine models development of food allergy to seafood and egg has been shown to be related to raising gastric pH.^{11,12} In addition, other authors have found an association between antacid medication and childhood asthma.¹³

We felt it was important to determine if the relationship between antacid medication and food allergy would be indicated in children, because the prevalence of food allergy is typically greater in young children. We hypothesized that parental report of antacid medications in children will be associated with an increased prevalence of physician-diagnosed food allergy in children and conducted a pilot study.

METHODS

Study Design

We used a cross-sectional study design to test our hypothesis. The primary outcome measure was whether parental report of treatment with antacid medication was associated with increased prevalence in physician-diagnosed food allergy.

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Secondary measures include (1) determining if age at initiation of antacid therapy or duration of antacid therapy are associated with increased prevalence of development of food allergy and (2) determining if there was a difference in parental report of prevalence of life-threatening food reactions, total IgE levels, or specific IgE levels between those treated and untreated with antacid medications. We collected questionnaires by convenience, sampling from a population of children seeking care at an allergy clinic.

Subjects

A suggested sample size of 114 was obtained using a power calculation (8% prevalence rate, an α of 0.05, and 95% confidence level). All children (birth to 18 years of age) presenting to the Emory Children's Center Allergy-Immunology Clinic for evaluation for atopic diseases (asthma, allergic rhinitis, atopic dermatitis, asthma, and food allergy) from 2009 to 2010 were eligible for inclusion. Exclusion criteria were children with chronic illness other than atopic diseases, including eosinophilic esophagitis without evidence of IgE-mediated food allergy, and those not giving informed consent.

Study Definitions

Food allergy was defined as a reaction consistent with anaphylaxis according to the symposium on the definition and management of anaphylaxis summary statement¹⁴ and food-specific IgE (either serum food-specific IgE or skin-prick test) or positive open graded food challenge as per practice parameters.¹⁵ We used a narrow case definition for food allergy (*i.e.*, only including children with clear history of anaphylaxis to foods and evidence of sensitization to that food) to reduce misclassification error. Children were separated into two categories: (1) food allergy as previously defined and (2) no history of food allergy. Children with reactions to food that did not meet definition for anaphylaxis or positive testing with no known reaction to food were excluded from the analysis.

Questionnaire

Parent(s) or guardian(s) of all children were asked to complete a questionnaire with 15 questions that included information on age, gender, diagnosis of GER, treatment with antacid medication (ever being treated with antacid medication, current treatment with antacid medication, type of antacid medication, age antacid medication was started, and duration of treatment with antacid medication), diagnosis of food allergy, report of previous history of life-threatening reaction to a food, and reported physician diagnosis of atopic conditions (atopic dermatitis, allergic rhinitis, and asthma).

Additional Data Collected

Information relating to the history of previous reactions to foods was obtained during clinic visit. Total IgE and food-specific IgE determination (egg, milk, peanut, shrimp, soy, and wheat) by skin-prick testing and/or serum food-specific IgE, and outcome of open graded food challenges were obtained from the chart and other clinical records by the primary investigator independently of the completion of the questionnaire in an attempt to blind the investigator to the results of the questionnaire. We also attempted to correlate the data as reported by the parents with the information on the chart when possible.

Institutional Review Board Considerations

The study was approved by the Emory University Institutional Review Board. Informed consent was obtained from the parent(s)/guardian(s) of all children participating in the study, verbal assent was obtained from children 6–10 years old, and written assent was obtained from children 11–17 years old.

Statistical Analysis

Means and frequency percents were calculated. Continuous data were examined for normal distribution. Data that were not normally distributed (total IgE level and specific IgE level) were log transformed before analysis and the antilog of the results were presented.

Chi-square (dichotomous data) and *t*-test (continuous data) were used to determine differences between those with and without a history of treatment with antacid medication. Crude prevalence ratio of parental report of history of treatment with antacid medication and food allergy and no food allergy was calculated.

An adjusted model was used to identify factors associated with prevalence of food allergy. The dependent variable was food allergy category (food allergy or no food allergy) and the independent variables included parental report that child was treated with antacid medication, age, gender, and history of atopic dermatitis. Variables included in the initial model were guided by previous knowledge of association with food allergy (*e.g.*, young age and history of atopic dermatitis). We removed the least significant variable using a backward elimination method until identifying the most parsimonious model. We also evaluated for confounding and interaction. Confounding was defined as >10% difference between the crude and adjusted estimate for that variable. We included all interaction terms (between exposure and all other variables of interest) to evaluate for interaction and used a value of $p < 0.05$ to define significant interaction.

An ANOVA analysis was used to determine differences in age at initiation of and length of therapy with antacid medication between those with food allergy

Table 1 Demographic and background data*

All Participants	Population Distribution <i>n</i> (%)	Population that had ever taken antacid medication (<i>n</i> = 47; %; 95% CI)	Population of those with food allergy (<i>n</i> = 45; %; 95% CI)
Overall population	104 (100)	45%	45%
Diagnosis of food allergy?			
Yes	45 (43)	57 (46–74)	
No	59 (57)	32 (22–46)	
Ever having taken antacid medication?			
Yes	47 (45)		57 (43–72)
No	57 (55)		32 (20–44)
Child's age			
≤5 yr old	44 (42)	40 (28–53)	57 (42–71)
>5–10 yr of age	34 (33)	55 (40–70)	35 (19–51)
≥10 yr of age	26 (25)	27 (12–41)	31 (13–49)
Child's gender			
Female	32 (31)	46 (31–62)	47 (30–64)
Male	72 (69)	39 (29–49)	42 (30–53)
Percent of population with atopic dermatitis			
Yes	66 (63)	41 (30–51)	55 (43–67)
No	38 (37)	50 (33–67)	23 (8–37)
Percent of population with asthma			
Yes	69 (66)	43 (33–53)	45 (33–57)
No	35 (34)	43 (27–59)	34 (17–52)
Percent of population with allergic rhinitis			
Yes	46 (44)	43 (29–56)	50 (36–64)
No	58 (56)	43 (29–56)	33 (20–47)

*Data represents mean ± SD or frequency (%).

and no food allergy. Chi-square (dichotomous data) and *t*-test (continuous data) were used to determine differences between those with a history of treatment with antacid medication and those without a history of treatment with antacid medication including percent of the population with food allergy, age at diagnosis of food allergy, length of diagnosis with food allergy (years), percent of the population with a history of life-threatening reactions to food, total IgE, and food-specific IgE. All statistical analyses were computed using SAS 9.2 or OpenEpi.¹⁶

RESULTS

One hundred four consecutive participants were invited to complete the questionnaire and 100% completed the questionnaire. Forty-five percent (47/104) had a parental report of treatment with antacid medication, and 43% (45/104) had a diagnosis of food allergy.

Demographic data are shown in Table 1. There was no significant difference in age, gender, or percent of population with atopic diseases (atopic dermatitis, asthma, and allergic rhinitis) between those who had ever been treated with antacid medications and

those not treated. Children with a history of ever taking an antacid medication had a greater prevalence of food allergy at 57% (27/47) versus 32% (18/57; *p* = 0.008).

Crude prevalence ratio for factors potentially associated with prevalence of food allergy are presented in Table 2. Children with a history of treatment with antacid medication had greater prevalence of having food allergy. Crude prevalence ratio was 1.8 (1.2, 2.9). Age of ≤5 years (crude prevalence ratio, 1.7 [1.1, 2.6]) and history of atopic dermatitis (crude prevalence ratio, 2.5 [1.2, 4.9]) were also associated with greater prevalence of food allergy. All other variables examined were not associated with an increase in prevalence of food allergy.

The results of the adjusted model are shown in Table 2. History of ever having an antacid medication was associated with increased prevalence of food allergy (adjusted prevalence ratio, 1.7 [1.1, 2.5]). Atopic dermatitis was also associated with an increased prevalence of food allergy (adjusted prevalence ratio, 2.4 [1.2, 4.7]), and age (≤5 years of age) was associated with an increased prevalence of food allergy (adjusted prevalence ratio, 1.5 [1.03, 2.2]).

Table 2 Factors associated with prevalence of food allergy

	Crude Prevalence Ratio (95% CI)	Adjusted Prevalence Ratio (95% CI)
History of taking antacid medication		
Yes	1.8 (1.2, 2.9)	1.7 (1.1, 2.5)
No (reference)	1 (—)	1 (—)
History of atopic dermatitis		
Yes	2.5 (1.2, 4.9)	2.4 (1.2, 4.7)
No (reference)	1 (—)	1 (—)
Age ≤5 yr of age		
Yes	1.7 (1.1, 2.6)	1.5 (1.03, 2.2)
No (reference)	1 (—)	1 (—)

There was no difference in age at initiation of therapy with antacid medication (2.7 ± 4.8 years versus 2.8 ± 3.4 years; $p = 0.13$) or length of therapy with antacid medication (1.2 ± 1.8 years versus 1.3 ± 2.0 years; $p = 0.15$) between those with food allergy and those with no diagnosis of food allergy. We were unable to analyze data related to type of antacid medication prescribed because of lack of parental responses and missing data. Data are not presented.

Results of the analysis of the subgroup of individuals with food allergy ($n = 45$) are presented in Table 3. Individuals who had ever taken an antacid medication had a higher mean peanut-specific IgE than those who had never taken an antacid medication (11.0 ± 5.0 versus 2.0 ± 5.5 ; $p = 0.01$). We found no difference in percent of food-allergic individuals reporting life-threatening reactions to food; percent of population that are allergic to egg, milk, peanut, shrimp, soy, or wheat; total IgE levels or food-specific IgE levels to milk, egg, wheat, soy, or shrimp between individuals reporting ever being treated with antacid medication and those never being treated with antacid medications.

DISCUSSION

This cross-sectional study in children shows that treatment with antacid medication was associated with increased prevalence of food allergy and higher levels of peanut-specific IgE. The importance of these data is that it strengthens the link between increased gastric pH and development of food allergy in humans and has implications for clinical practice. Previous studies have shown an association between treatment with antacid medication and development of food sensitization (*i.e.*, positive skin tests and/or specific IgE) in

human adults and mice.^{10–12} In a study of 153 adults treated for 3 months with H₂-blockers or PPI it was shown that 5/153 (3.3%) developed hazelnut-specific IgE and 3/153 (1.9%) had a positive oral food challenge to hazelnuts when compared with that found in the general population (0.2–0.7%).¹⁰ Using murine models of food allergy, it has been established that administration of antacid medication is crucial for the development of reactivity (reduced rectal temperature) after food challenge.^{10,12} Our data also lend support to the idea that treatment with antacid medication is associated with development of food allergy in children.

A recent abstract examining the effect of H₂-blockers in a population of 259 children did not find any relationship between antacid use and food allergy.¹⁷ There are important differences between that analysis and the one reported here. That population was obtained mostly from the general pediatric clinic while this population was obtained from an allergy-immunology clinic and enriched for atopy, and they focused on use of H₂-blockers and did not examine the effect of PPI's. There is some evidence that the histamine receptor gene is important in allergy^{18–20} and that stimulation *via* the histamine H₂-receptor reduces both eosinophil and neutrophil chemotaxis,²¹ enhances IL-10 production,²² inhibits IL-13 production,²³ and inhibits proliferation of both Th1 and Th2 T cells.²³ It has been hypothesized that the H₂-receptor may be an important regulator of H₁-receptor-induced allergic inflammation. We would have liked to look at the difference in effect between H₂-blockers and PPIs but were unable to do this because of the small numbers, lack of access to pharmacy data, and inability to collect this data by recall because many parents were unable to remember the name of the medication used.

The association between antacid medication and food allergy could also be caused by reverse causation (*i.e.*, the food allergy causing the reflux). This seems unlikely because IgE-mediated allergy is unlikely to cause isolated GER without affecting other organ systems. In addition, only individuals with a history of anaphylaxis to food were included to help exclude other types of food intolerances or mild sensitivities to food.

We were only able to replicate the increase in IgE levels that has been reported by other authors for peanut-specific IgE.^{9–11} We did not find any differences in total IgE or other food-specific IgE (milk, wheat, soy, or shrimp) between those reporting treatment with antacid medication and those with no exposure to antacid medication.

This pilot study was not designed or powered to detect these differences, and the numbers of participants with complete laboratory data was small.

Threats to internal validity include exposure (history of treatment with antacid medications) that was deter-

Table 3 Subgroup analysis of participants with food allergy ($n = 45$) by history of treatment with antacid medication

	Never Had Antacid Medication*	History of Ever Taking Antacid Medication*	<i>p</i> Value
<i>n</i>	18	27	
Age (yr)	5.6 ± 5.1	6.1 ± 2.9	0.7
Age (yr) at diagnosis of food allergy#	2.4 ± 2.7	2.0 ± 1.6	0.6
Time (yr) since diagnosis of food allergy	1.3 ± 3.0	3.0 ± 2.0	0.6
Egg allergic <i>n</i> (%)	6/18 (33%)	14/27 (52%)	0.2
Milk allergic <i>n</i> (%)	8/18 (44%)	11/27 (41%)	0.8
Peanut allergic <i>n</i> (%)	12/18 (67%)	13/27 (48%)	0.2
Shellfish allergic <i>n</i> (%)	7/18 (39%)	4/27 (11%)	0.07
Soy allergic <i>n</i> (%)	3/18 (17%)	6/27 (22%)	0.7
Wheat allergic <i>n</i> (%)	2/18 (11%)	6/27 (22%)	0.3
Percent with history of life-threatening reactions to food	8/18 (44.4%)	15/26 (56%)§	0.7
Food allergy considered severe by parent	11/16 (69%)§	18/24 (75%)¶	0.6
Total IgE#	164 ± 4.1	244 ± 4.5	0.5
IgE Egg#	2.2 ± 12.2	3.3 ± 5.5	0.7
IgE Milk#	1.3 ± 20.1	7.4 ± 6.7	0.2
IgE Peanut#	2.0 ± 5.5	11.0 ± 5.0	0.01
IgE soy	4.3 ± 5.0	0.7 ± 0.5	0.2
IgE shrimp#	2.7 ± 5.5	4.3 ± 24.5	0.8
IgE wheat#	1.5 ± 7.4	2.2 ± 6.7	0.7

*Data represent mean ± SD or frequency (%).

#Log transformed before analysis.

§Two missing response.

¶Three missing responses.

mined in a retrospective fashion using parental report (possibly introducing recall bias and making determination of whether the exposure preceded the disease difficult), the definition of food allergy was not based on double-blind placebo-controlled food challenges (possibly adding misclassification bias), the fact the questionnaire was not validated and did not include information regarding temporal association between taking the antacid medication and the food allergy reaction, and the small numbers. We were unable to do further analysis on the subgroup that was currently taking antacid medication because of small numbers ($n = 15$). Generalization is also limited because of the fact that this is a pediatric population obtained from a tertiary care center allergy clinic that specializes in diagnosis and management of food allergy and the population consisted of children with a personal or family history of atopy.

We feel that the results from this pilot study are valid because the analysis indicates that report of treatment with antacid medication was independently associated with development of food allergy, and the data are in line with what previous authors have found in both murine and human studies.

The results also have biological plausibility, although the data are unable to elucidate the mechanism. Eating is a complicated and delicate balance between tolerance and immune response.²⁴ Normally, immunologic responses to food protein in the gastrointestinal (GI) tract are mediated by multiple factors including the strong physical barrier of the GI epithelium, digestive processes (pH and proteolytic enzymes), T cells in the lymphoid gut tissue, and secretory IgA.²⁴ Together, these processes lead to a general immunosuppressed/tolerant environment in the GI tract. Any abnormalities in this balancing act, such as that seen by the addition of antacid medication, may lead to lack of tolerance and development of food allergy. Increasing stomach pH could lead to conformational changes in important food allergen epitopes and does lead to decreased efficiency of pepsinogen activation. Any resultant changes in protein structure (either conformational or *via* protein digestion) could lead to enhanced binding (humoral or cellular) and increased recognition.

The data support the need for prospective studies (clinical and mechanistic) to determine the effects of treatment with antacid medication on development of food allergy and the biological mechanism responsible

for this association. The clinical studies should address some of the questions this study raises: (1) will the relationship be maintained in a more rigorous, prospective study; (2) is the increased prevalence across all populations or just those with a personal/family history of atopy; (3) is the effect due to treatment with antacid medication or the GER itself; (4) is this effect related to any antacid medication or just to one class (such as H₂-blockers or PPIs).

Additional mechanistic studies are necessary to define the mechanism by which antacid medications predispose to the development. If a relationship between treatment with antacid medication and development of food allergy can be clearly be established, clinicians will need to consider the risk of development of food allergy with the benefits from treating GER when starting a child on antacid medications.

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