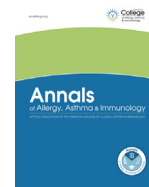




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Effects of allergen sensitization on response to therapy in children with eosinophilic esophagitis

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ABSTRACT

Background: In children with eosinophilic esophagitis (EoE) foods are the most common disease triggers, but environmental allergens are also suspected culprits.

Objective: To determine the effects of environmental allergen sensitization on response to treatment in children with EoE in the southeastern United States.

Methods: Patients 2 to 18 years old who were referred to the Arkansas Children's Hospital Eosinophilic Gastrointestinal Disorders Clinic from January 2012 to January 2016 were enrolled in a prospective, longitudinal cohort study with collection of demographics, clinical symptoms, medical history, allergy sensitization profiles, and response to treatment over time. Comparisons were made between complete responders (peak esophageal eosinophil count <15 per high-power field [HPF]) and nonresponders (>25 eosinophils per HPF) after treatment with diet elimination alone, swallowed corticosteroids alone, or diet elimination and swallowed corticosteroids. Sensitization patterns to environmental allergens found in the southeastern United States were analyzed for the effect on treatment response.

Results: A total of 223 individuals were enrolled. Of these, 182 had environmental allergy profiling and at least one endoscopy while receiving proton pump inhibitor (PPI) therapy. Twenty-nine individuals had PPI-responsive EoE and were excluded from further analysis, leaving 123 individuals with non-PPI-responsive EoE who were further analyzed; 72 (58.5%) were complete responders and 33 (26.8%) were nonresponders. Seventeen individuals (13.8%) were partial responders (≥ 1 but ≤ 25 eosinophils per HPF) and excluded from further analysis. Nonresponders were more likely to be sensitized to perennial allergens ($P = .02$). There was no significant difference in response based on seasonal allergen sensitization. Individuals with mold or cockroach sensitization were more likely to fail combination diet and swallowed corticosteroid treatment ($P = .02$ and $P = .002$).

Conclusion: Perennial allergen and mold sensitization may lead to nonresponse to EoE treatment in some patients. Additional studies are needed to further understand the effect of environmental allergens on EoE.

Trial Registration: [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01779154) identifier: NCT01779154.

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Introduction

Eosinophilic esophagitis (EoE) is an increasing clinical problem. Estimates of prevalence in the United States have increased from 2.3 per 100,000 population in 1976 to 25.9 per 100,000 population in 2015, with even higher rates reported in some populations.^{1–4} Characterized by eosinophilic inflammation of the esophagus, affected patients may experience a variety of clinical symptoms that lead to increased health care use and decreased quality of life.⁵ Diagnostic options are limited to repetitive endoscopy, whereas treatment is centered on use of swallowed corticosteroids or diet restrictions. Although food remains the most common trigger,^{6,7} the role of aeroallergens in the development of EoE has also been questioned. Several studies have found changing clinical symptoms during peak pollen seasons, especially in those with concomitant allergic rhinitis.^{8–10} The frequency of diagnosis also appears to increase during pollen seasons, with a lower frequency found in winter.^{11–14} However, other studies have found no clear link among aeroallergen sensitization, symptom onset, and seasonal diagnosis of EoE.^{15–18}

Most EoE studies have been completed in urban populations. It is unclear whether there are differences in disease presentation and response to management in rural or other nonurban populations.^{16,18–20} As such, characterization of different patient populations is important to obtain a clearer understanding of the disease process and to optimize management strategies. In 2015, 42% of Arkansas' population lived in nonurban areas vs 15% for the US population as a whole. This nonurban population has not been described compared with those living in other environments.²¹ The purpose of this study was to determine the effects of seasonal and perennial allergen sensitization on the response to treatment in a pediatric population with EoE living in the southeastern region of the United States.

Methods

Patient Inclusion

Patients 2 to 18 years of age who were referred to the Arkansas Children's Hospital multispecialty Eosinophilic Gastrointestinal Disorders Clinic from January 2012 to January 2016 were considered for enrollment. Patients were required to have had at least one esophageal endoscopy with findings of 15 eosinophils per high-power field (HPF) or more at 40× magnification on at least one esophageal biopsy specimen as reviewed by a board-certified pathologist (R.A.L.). Patients were then consented and enrolled in a prospective, longitudinal cohort with collection of data, including demographics, clinical symptoms, medical, family, and diet history, allergy profiles, and response to treatment over time. The study was approved by the University of Arkansas for Medical Sciences Institutional Review Board. Written consent was obtained from each study participant.

Allergy Profiling

Environmental allergen sensitization was determined through use of skin prick testing (SPT) and/or serum specific IgE testing (ImmunoCAP, Phadia AB, Uppsala, Sweden). SPT was performed using the Greer Pick Single Site Allergy Skin Test System (Greer Labs, Lenoir, North Carolina) with histamine and saline controls. Testing to perennial allergens included dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), cat hair (*Felis catus domesticus*), dog epithelia (*Canis* species), cockroach (*Periplaneta americana*), and mold (*Aspergillus*, *Alternaria*, *Cladosporium*, and *Curvularia*). Seasonal allergens included trees (elm, white ash, eastern oak, hickory/pecan, black walnut, birch, mountain cedar, and cottonwood), grasses (Bermuda, Bahia, fescue, Johnson, and timothy), and weeds (ragweed, pigweed, dock/sorrel, marsh elder,

plantain, and hemp) found throughout the southeast region of the United States. Individual test results were considered positive if the individuals had a SPT wheal size of 3 mm or larger than the negative control and/or a serum specific IgE level of 0.35 kU/L or higher. Allergy testing was performed at the initial EoE visit to the standard panel of environmental allergens in all patients unless declined by the patient or family. Previous allergy testing completed during the 2 years before visit or enrollment was also accepted. For most patients, allergy testing was performed before the initiation of EoE treatment. Allergy testing performed after initiation of EoE treatment was also accepted. Responses to management were compared between patients with seasonal, perennial, and/or mold sensitization and those with no sensitization.

Response to Treatment

Response to treatment, including response to proton pump inhibitors (PPI), dietary manipulation, and/or use of swallowed corticosteroids, was assessed. All patients were assigned to at least 8 weeks of PPI therapy with follow-up endoscopy to assess PPI responsiveness. Dosing of PPI was based on physician preference. For those in whom PPI treatment failed, management decisions were based on physician and parental preference using diet elimination alone, swallowed corticosteroids alone, or a combination of both diet elimination and swallowed corticosteroids. If diet manipulation was chosen, the patient was placed on allergen-specific elimination (single allergen elimination or combination allergen elimination based on allergy testing and clinical history), 6-food elimination (milk, egg, soy, wheat, peanut or tree nuts, fish or shellfish), or elemental diet using an elemental formula alone. Patients then received one-on-one dietary counseling provided by a trained dietician. If swallowed corticosteroids were chosen, the patients were given budesonide (dosing range, 0.25–1 mg twice daily) or fluticasone propionate (220–880 µg twice daily). If budesonide was used, patients were instructed to mix each 2-mL respule with 4 packets of a sugar substitute (Splenda). If fluticasone propionate was chosen, patients were instructed to spray the inhaler directly into the mouth and swallow. Patients were also instructed to avoid eating or drinking for 30 minutes after taking the medication.

Patients continued to receive treatment for at least 10 to 12 weeks before additional endoscopy was performed. Patients were considered complete responders if the peak esophageal eosinophil count was less than 15 eosinophils per HPF and nonresponders if the peak esophageal eosinophil count was greater than 25 eosinophils per HPF. Patients with peak eosinophil counts greater than 15 eosinophils per HPF but less than 25 eosinophils per HPF were considered partial responders but were excluded from further analysis. Symptom improvement was not used as a measure of response to treatment.

Statistical Analysis

All demographics and clinical outcomes were summarized using mean (SD) for continuous variables and frequency (percentage) for categorical variables. Categorical variables in 2 independent groups were compared using a Fisher exact test. Continuous variables in 2 independent groups were compared using the Wilcoxon rank-sum test. Paired categorical outcomes with more than 2 categories were compared using the Bowker test of symmetry. Effects for dichotomous outcomes were summarized using odds ratios (ORs) and 95% confidence intervals (CIs). All tests conducted were 2-sided, assuming a significance level of 5%. All statistical analyses were performed using the software R, version 3.0.2. Descriptive tables were generated using the Regression Modeling Strategies package.

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