

**THE SEASONALITY OF EOSINOPHILIC ESOPHAGITIS FLARES IN CHILDREN
AND ADOLESCENTS IN ARIZONA**

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Kelsi Manley

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Mentor: Dana Williams, MD

ABSTRACT

Objectives: Aeroallergens are implicated in the pathogenesis of eosinophilic esophagitis, which has a recurrent or relapsing nature. We aim to determine the incidence of seasonal disease recurrence, referred to as flares, of eosinophilic esophagitis in patients in Arizona with eosinophilic esophagitis in remission, and to characterize the presence of allergy and other disease co-morbidities in patients that experience disease flare.

Methods: A retrospective study was performed by analyzing data from visits of patients aged 5 to 18 years coded for eosinophilic esophagitis in remission seen by the Phoenix Children's Hospital Pediatric Gastroenterology Department between June 2010 and June 2011. The data included 148 patients and 326 clinical visits. Data identified demographic information, allergy, and other disease co-morbidities. Arizona seasons were defined as: spring from February 15 to June 15, and fall from September 1 to November 30, according to the typical pattern of allergen pollination. To analyze incidence and season of flares, statistical methods used included the Chi-square tests and logistic regressions.

Results: Ninety-four of 148 patients (63.5%) flared during the study period. An increased incidence of flares in the fall compared with other seasons was statistically significant ($p = 0.041$). Flares in the spring also had an increased incidence. Of the 94 patients that flared, 70 patients (74.5%) had environmental allergy, 83 (88.3%) had food allergy, and 66 (70.2%) had both environmental and food allergy.

Conclusions: Our findings suggest a role for seasonal environmental allergens in the pathogenesis of eosinophilic esophagitis and disease flares in children in Arizona, particularly those with food allergy, environmental allergy, or both.

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INTRODUCTION

Eosinophilic esophagitis (EoE) is a clinicopathologic disorder of the esophagus characterized by upper gastrointestinal symptoms in association with esophageal eosinophilia. Initially thought to be gastroesophageal reflux disorder (GERD) refractory to GERD management, EoE is now known to be a separate entity with diagnosis now requiring exclusion of PPI-responsive esophageal eosinophilia. Updated consensus recommendations in 2011 describe EoE as a “chronic, immune/antigen-mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation”¹. Due to the chronic nature of the disease, symptoms may be persistent or relapsing. A strategy for optimal surveillance has not been formally established. Many pediatric gastroenterologists assess symptoms at regularly scheduled visits and perform endoscopies either based on symptoms or periodically in those who are asymptomatic or with recent treatment change. Therapeutic intervention consists of dietary restriction, topical corticosteroid application, or a combination of both. Changes in therapy are guided by clinical and pathological findings. An increase in incidence and prevalence has been noted, due both to increased recognition and to the chronic nature of EoE with lack of associated mortality^{2,3}.

The pathogenesis of EoE is likely multi-factorial, with contribution from genetic and environmental factors. Accumulating evidence suggests a TH2-mediated pathogenesis, with demonstrations of overexpressed interleukin-13 and induced eotaxin-3 supporting the immunologic basis of EoE^{4,5} and suggesting the presence of esophageal eosinophils represents an allergic response directed toward extracellular antigens. An allergic component is further supported based on co-existing atopic conditions in the majority of patients with EoE^{6,7}. Food allergies are well known to play a role in EoE based both on antigen testing and resolution of clinical and histologic abnormalities with dietary removal of antigens⁸⁻¹¹.

While not as prominently as food allergens, aeroallergens have been implicated in the pathogenesis of EoE as well. Aeroallergen sensitization is associated with EoE via induction of esophageal eosinophilia in mice following intranasal exposure to mold and dust mite allergen¹². Relevance that these findings may be applicable to humans comes from Fogg et al who

describe a patient with aeroallergen sensitivity and EoE, whose exacerbation and resolution of symptoms and eosinophilia correlate with seasonal aeroallergen exposure¹³. Seasonality of symptoms and diagnosis of EoE is described in various studies, with both prominent in times of year when aeroallergens are highest, further suggesting a role of aeroallergens^{3,14-16}.

The seasonal variability of symptom onset, seasonal intensity of eosinophilia, seasonal distribution of new diagnoses of EoE and correlation between time of new diagnoses and pollen count have been characterized^{15,16}. These characteristics have been studied in the eastern and midwestern United States (Washington, D.C., Indiana, Minnesota) as well as internationally (Turkey). In the literature, however, the relationship between environmental aeroallergens and disease relapses has not been documented. There is also no published work to date from the southwestern United States, distinguished from other regions of the country by its unique desert allergen profile.

Of the five allergen categories (food, common ragweed, mold, house dust mites, and cats/dogs), Phoenix ranks second of thirty cities in allergen sensitization based on quantitative measurement of circulating IgE to specific allergens¹⁷. Phoenix Children's Hospital is a tertiary facility that provides the most comprehensive pediatric care in Arizona. The Phoenix Children's Hospital Pediatric Gastroenterology Department is a large division that consists of fifteen pediatric gastroenterology providers with observed clinical and histologic relapses in a large population of pediatric EoE patients. This is the first study of its kind in the southwest United States.

METHODS

A retrospective review of the Phoenix Children's Hospital billing database, MedAptus, was performed to identify patients with a diagnosis of EoE. The database was searched for outpatient clinic visits from June 2010 to June 2011. Inclusion criteria consisted of patients who were age 5 to 18 years with ICD-9 code 530.13 up to the third diagnosis in billing performed by pediatric gastroenterology providers. Each medical chart identified through coding was reviewed to confirm the diagnosis of EoE based upon history of symptoms of dysphagia, choking, gagging, regurgitation, globus, odynophagia, nausea, emesis, abdominal pain, chest pain, burning sensation, and/or weight loss and based upon history of 15 or more eosinophils per high powered field on esophageal biopsies. Pre-treatment with proton pump inhibitors was not standard of care during the study period. Patients with newly diagnosed EoE or with EoE that was not in symptomatic or histologic remission prior to enrollment were excluded. Remission included either clinical remission with absence of symptoms in a previously symptomatic patient or histologic findings of fewer than 15 eosinophils per high powered field. Patients were also excluded if they were incorrectly coded with a diagnosis of EoE, if their medical records were incomplete, or if they were in the hospital for alternate reasons. During chart review of the electronic medical records, data regarding patient demographics, symptoms, and co-existence of environmental allergy, food allergy, gastroesophageal reflux disease, autism, celiac disease, and inflammatory bowel disease was obtained, specifically from documentation of parental report, active problem or active diagnosis, or records from external allergy report. Information on esophagogastroduodenoscopy (EGD) results performed during the study period were recorded. Endoscopic findings were obtained through review of gastroenterologist operative reports in Clinical Outcomes Research Initiative software, and histologic findings were obtained from pathologist reports. Pathology studies were not re-reviewed for purposes of the study. This study was approved by the Phoenix Children's Hospital Institutional Review Board (IRB #12-015).

Utilizing EoE ICD-9 code 530.13, search of the MedAptus database identified a total of 196 patients that had 558 total visits, composed of ambulatory visits and procedures, during the study period. Of these, 31 patients were excluded due to absence of disease remission, 5 due to incorrect coding of EoE as a diagnosis, 7 due to the patient visit being unrelated to EoE, and 5 due to an incomplete medical record. From the remaining medical charts, visits that were within an eight week period were combined to represent one visit. With these criteria, 148 patients were characterized over 326 visits.

Each of the 326 visits was reviewed and categorized as a visit associated with an EoE flare or a visit in which EoE was well-controlled, which was termed a control visit. Flare of EoE was defined as recurrence or worsening of symptoms of dysphagia, odynophagia, food impaction, abdominal pain, feeding refusal or severe food selectivity expressed by the patients or observed by the parents, or by histologic findings of eosinophilic count greater than 15 per high powered field in a patient previously in remission. Patients were then separated into two groups: the control group consisted of individuals who did not experience flare as defined by the above criteria during the study period, and the study group consisted of individuals who did experience disease flare during the study period. We recorded the season of flare occurrence, with Arizona seasons defined as: spring from February 15 to June 15, and fall from September 1 to November 30, according to the typical pattern of allergen pollination^{18,19}.

The data set underwent comprehensive data cleaning and recoding for analysis. For the descriptive analysis of the data set, quantitative variables were given dependent on the underlying distribution as mean (standard deviation) or median (range). For qualitative variables, relative frequencies were computed. For the univariate influence of risk factors on flares, a chi-square or exact Fisher's test was used. The multivariate impact of risk factors on outcome was assessed with a logistic regression model. The incidence rates were compared with a binominal test. Pairwise comparisons were corrected using the Bonferroni method.

Table 1 – Table of Study Population Demographics/Characteristics, n = 148

Characteristics	Summary Description, n = 148 n (%)
Age, years	Range 5-18, average 10.8, SD 3.9
Gender	
Male	101 (68.2)
Female	47 (31.7)
Environmental Allergy	101 (71.6)
Food Allergy	127 (85.8)
Environmental and Food Allergy	98 (66.2)
GERD	37 (25)
Autism	13 (8.8)
Celiac Disease	5 (4.1)
Inflammatory Bowel Disease	2 (1.4)

SD = standard deviation

RESULTS

Our patient population was aged 5 to 18 years (mean age 10.8 years, standard deviation 3.9 years) and included 101 males (68.2%) and 47 females (31.7%). One hundred and six of the study population (71.6%) had environmental allergy, 127 (85.8%) had food allergy, 98 (66.2%) had both environmental and food allergy. Thirty-seven patients (25.0%) had gastroesophageal reflux, thirteen patients (8.8%) had autism, six patients (4.1%) had celiac disease, two patients (1.4%) had inflammatory bowel disease. The demographic details of the study population is presented in Table 1.

Of our 148 patients, 94 patients (63.5%) experienced a flare during the study period. They were aged 5 to 18 years with mean age and standard deviation the same as the study population, 10.8 years and 3.9 years, respectively. Those that flared included 62 males (66.0%) and 32 females (34.0%). Of the 94 patients that flared, 70 patients (74.5%) had environmental allergy, 83 (88.3%) had food allergy, and 66 (70.2%) had both environmental and food allergy. The demographic details of the EoE population that flared are presented in Table 2.

In contrast to the study population that flared, 54 of our 148 patients (36.5%) did not experience an EoE flare during the study period. These patients were aged 5 to 17 years with mean age 10.9 years and standard deviation of 3.8 years. Those that did not flare included 39 males (72.2%) and 15 females (27.8%). Of the 54 patients that did not flare, 36 patients (34.0%) had environmental allergy, 44 (34.7%) had food allergy, and 32 (32.7%) had both environmental and food allergy. The demographic details of the EoE population that did not experience flare is presented in Table 2.

Table 2 – Characteristics of Flare Group Versus Control Group

Characteristics	Control Group, n = 54 (36.5) n (%)	Flare Group, n = 94 (63.5) n (%)	P value
Age, years	Range 5-17, mean 10.9, SD 3.8	Range 5-18, mean 10.8, SD 3.9	
Gender			
Male	39 (72.2)	62 (66.0)	
Female	15 (27.8)	32 (34.0)	
Environmental Allergy	36 (66.7)	70 (74.5)	0.31
Food Allergy	44 (81.5)	83 (88.3)	0.25
Environmental and Food Allergy	32 (59.3)	66 (70.2)	0.56

SD = standard deviation

Regarding the co-morbidities of the study population, of the 37 patients with gastroesophageal reflux, 19 patients (51.4%) flared and 18 patients (48.7%) did not flare. Of the 111 patients without gastroesophageal reflux, 75 patients (67.6%) flared and 36 patients (32.4%) did not flare. Of the 13 patients with autism, 6 patients (46.2%) flared and 7 patients (53.9%) did not flare. Of the 135 patients without autism, 88 patients (65.2%) flared while 47 patients (34.8%) did not flare. Five of the 6 patients (83.3%) with celiac disease flared and both of the two patients (100%) with inflammatory bowel disease flared.

Of the 326 visits during the study period, 144 visits (44.2%) were flare visits and 182 visits (55.8%) were control visits. Each visit could occur in the fall (defined as September 1 through November 30), spring (defined as February 15 through June 15), or other season (defined as the remainder of the year not encompassed by fall or spring season). A visit that occurred in the fall was more likely to be a flare visit than one that occurred in the spring or other season; 34 of 66 visits (51.5%) in the fall were flares, whereas 48 of 114 spring visits (42.0%) and 62 of 146 other season visits (42.0%) were flares (Figure 1). The odds ratio of a flare during the fall versus other season was 1.856 ($p = 0.08$); the odds ratio of a flare during the spring versus other season was 0.819 ($p = 0.155$) (Table 3). The incidence of flare visits in each season with correction for the differing lengths of season was highest in the fall with an incidence of 7.4% (p value = 0.041). The incidence of flare visits in spring was 6.6% and the incidence for other season was 6.5%. When reviewed by month, flare occurrence was greatest in October, with 18 of 28 visits (64.3%) that month associated with flare, followed by April, with 17 of 29 visits (58.6%) in April associated with flares. The flare occurrence in two months of June are documented, at the beginning and end of the study period. In June 2010, 11 of 21 visits (52.4%) are flare visits; in June 2011, 12 of 33 visits (36%) are flare visits.

Figure 1: Fall vs. Other Season Flares

	Seasonal Distribution Odds Ratios	
	Odds Ratio	p-Value
Fall vs. Other Months (spring excluded)	1.856	0.041
Spring vs. Other Months (fall excluded)	0.819	0.155

Table 3 – Co-Morbidities in Flare Versus Control Groups

Co-Morbidities, n	Flare, n (%)	No Flare, n (%)
GERD, 37	19 (51.4)	18 (48.7)
Autism, 13		
Celiac Disease, 6	6 (46.2)	7 (53.9)
Inflammatory Bowel Disease, 2	5 (83.3)	1 (16.7)
	2 (100)	0 (0.0)

DISCUSSION

We found that there is seasonal variation to the incidence of EoE flares in children in Arizona. The incidence of EoE flares in Arizona children is greater in the fall than in the spring and other season. When examined by month, the incidence of flares in October has an impressive peak, even in comparison to the other months that comprise the fall season. Similarly, the flare incidence in April is greater than the other months that comprise the spring season.

To explain this, we refer to the aeroallergen pollination pattern. In October in Arizona, Bermuda grass is scalped, rye grass is planted, and ragweed pollinates. In April in Arizona, all springtime trees, rye grass, and ragweed pollinate. Additionally, the introduction of pollens at the beginning of the seasons, in September for fall and in February and March for spring, prime the immune response, resulting in symptoms two to four weeks later, in October and in April. We can also hypothesize that patients who begin to experience symptoms in the earlier weeks of the season would contact the physician's office after a few weeks of symptoms and then await an appointment for another week or two. Thus, they would most likely be seen in October in the fall and April in the spring, although our data does not reflect an increase in visits during these two months compared to other months. This suggests a role for seasonal environmental allergens in the pathogenesis of EoE and EoE flares.

For patients that experienced a flare, a similar rate was seen between males and females. This is despite the higher prevalence of EoE in males, seen both in our study population and in the literature. A higher percentage of patients with environmental allergy flared compared to those who did not have environmental allergy, but this coincided with normal statistical variation rather than demonstrating statistical significant. Our data shows that patients with neither environmental nor food allergy are less likely to flare than patients with either one of these allergies. These findings suggest that EoE patients with environmental allergy experience more flares compared to those who are free of environmental allergy, and further supports the role of aeroallergens in the pathogenesis of EoE and EoE flares.

Interestingly, our data shows that EoE patients with GERD had a lower rate of flares than patients who do have not GERD. This finding may be due to patients or care providers

attributing symptoms which would otherwise represent an EoE flare to the co-existent GERD rather than to EoE. We also found it interesting that EoE patients with autism had a lower rate of flares than EoE patients without autism. This may again be secondary to care providers assuming symptoms are due to other GI-related issues or sensory obstacles attributable to autism itself rather than to EoE.

Of the 326 visits during the study period, there were more control visits than flare-related visits. We suspect that the number of control visits was greater as these accounted for the food challenges and surveillance visits.

The demographics of our patient population are consistent in many ways with what is seen in the existing literature. We saw a higher prevalence of EoE in males than females. The presence of environmental allergy and/or food allergy in our EoE population is also consistent with what is found in the literature. However, no literature to date has described the incidence or seasonality of EoE flares, nor the characteristics of patients that experience flares.

Our study is limited by its retrospective nature. The patients were not pre-treated with proton pump inhibitors prior to their diagnosis of EoE, which is now standard of care. We reviewed the pediatric pathologists' report of the esophageal biopsies, but did not re-examine the biopsy specimens nor collect the location along the esophagus at which the biopsies were obtained. We also experienced data deficiencies with allergy testing as there was inconsistent medical records and no coordination of care during our study period, but rather hospital-based gastroenterologists and community-based allergists, requiring dependence upon family report for information pertaining to allergy testing.

We did not characterize the patients that flared during the fall season versus those that flared during the spring or other season. We did not describe the characteristics of the flares as clinical, histologic, or both, in relation to the seasonality. We also did not attempt to identify management strategies to which those that flared responded, nor characterize treatment regimens that may have prevented flares from occurring in the control population. It is conceivable that the identification of patients at higher risk of flare and of the season in which flare is most likely to occur would assist care providers in implementing a medication-sparing

regimen that prevents flares. These directions could inspire future studies. Prospective studies that examine the desert-specific environmental allergen testing in relation to EoE flares and the regionality in EoE phenotypes are also needed.

In conclusion, we found a seasonal variation to the incidence of EoE flares in children in Arizona, with the incidence greater in the fall than in the spring and other season. We explain this with the aeroallergen pollination pattern. While not statistically significant, we noted a higher percentage of patients with environmental allergy flared compared to those who did not have environmental allergy. These findings support the role of aeroallergens in the pathogenesis of EoE and EoE flares.

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