



Contents lists available at ScienceDirect



Seasonal exacerbation of esophageal eosinophilia in children with eosinophilic esophagitis and allergic rhinitis

Gita Ram, MD^{*}; Juhee Lee, MD^{*}; Megan Ott, CRNP^{*}; Terri F. Brown-Whitehorn, MD^{*,†}; Antonella Cianferoni, MD, PhD^{*,‡}; Michele Shuker, RD^{*}; Mei-Lun Wang, MD^{†,§}; Ritu Verma, MD^{†,‡}; Chris A. Liacouras, MD^{†,‡}; and Jonathan M. Spergel, MD, PhD^{*,‡}

^{*} Division of Allergy and Immunology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

[†] Division of Gastroenterology and Nutrition, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

[‡] Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

[§] GlaxoSmithKline, Philadelphia, Pennsylvania

ARTICLE INFO

Article history:

Received for publication April 23, 2015.

Received in revised form July 2, 2015.

Accepted for publication July 6, 2015.

ABSTRACT

Background: Evidence supports a possible link between eosinophilic esophagitis (EoE) and environmental aeroallergens, which can manifest as seasonal exacerbation of esophageal eosinophilia. Few studies have examined this link in pediatric patients with EoE.

Objective: To identify the proportion of patients with seasonal induced esophageal eosinophilia.

Methods: A retrospective chart review was conducted of all patients diagnosed with EoE at the authors' institution. Demographic data were collected by chart review. Seasonal variation or flare was defined as a change from fewer than to at least 15 eosinophils per high-power field and a minimum of a 2-fold increase in eosinophil count between 2 consecutive biopsy specimens in different seasons without dietary or medication modifications.

Results: Of the 1,180 patients with EoE, 160 (14%) were suspected of having aeroallergen-associated triggers by history. Of these 160 patients, 32 (20%) had biopsy examination-confirmed variation of EoE triggered by aeroallergens. Most of these patients were boys (84%), all had a history or examination consistent with allergic rhinitis, and most had a history of asthma (75%). Thirty-two subjects had obvious seasonal variation, 22 of whom also had known food-induced symptoms.

Conclusion: Children with EoE and allergic rhinitis might have exacerbations in their esophageal eosinophilia during certain seasons depending on the specific aeroallergens to which they are sensitized. Identification of environmental allergens to sensitized patients is important and can guide therapy.

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Introduction

Eosinophilic esophagitis (EoE) is a chronic immune and antigen-mediated condition characterized by eosinophilic inflammation of the esophagus, without involvement of the rest of the gastrointestinal tract, resulting in esophageal fibrosis and dysfunction. The typical presentation varies by age group, with young children commonly presenting with feeding refusal or intolerance and older children presenting more commonly with abdominal pain, vomiting, or gastroesophageal reflux disease (GERD)-like symptoms.

Drs Ram and Lee and Ms Ott contributed equally to this work.

Reprints: Jonathan M. Spergel, MD, PhD, The Children's Hospital of Philadelphia, Perelman School of Medicine at University of Pennsylvania, 3550 Market Street, Philadelphia, PA 19104-4399; E-mail: spergel@email.chop.edu.

Disclosures: Authors have nothing to disclose.

Funding Sources: The Stuart Starr Endowed Chair of Pediatrics, the Children's Hospital of Philadelphia, the Joint Center for Gastroenterology and Nutrition of CHOP-HUP, and the CHOP Eosinophilic Esophagitis Family Research Fund.

Dysphagia and food impaction can be the presenting symptoms in adolescents and adults.¹ The major complications of EoE include failure to thrive, esophageal dysfunction, behavioral feeding problems, and esophageal strictures; thus, evaluation and chronic surveillance of these patients is important. The diagnosis of EoE requires symptoms of esophageal dysfunction and endoscopy with esophageal biopsy examination demonstrating at least 15 eosinophils per high-power field (eos/hpf). Patients must meet this criterion despite treatment with a high-dose proton pump inhibitor (PPI) for at least 6 to 8 weeks to rule out GERD or PPI-responsive esophageal eosinophilia as a cause for esophageal eosinophilia.¹

Eosinophilic esophagitis has been believed to be driven primarily by food allergens, most commonly milk, egg, soy, and wheat.^{2,3} Recently, there have been some studies suggesting that aeroallergens could play a role in the pathogenesis of esophageal eosinophilia in certain individuals. The correlation among esophageal eosinophilia, EoE, and aeroallergens was first introduced by Mishra et al⁴ who described the development of esophageal

eosinophilia in mice after intranasal exposure to *Aspergillus fumigatus*. They proposed a mechanism whereby allergen sensitization in the respiratory tract by intranasal exposure followed by topical delivery of the allergens to the esophagus leads to EoE. The authors reported the first clinically relevant case of true aeroallergen-associated esophageal eosinophilia in a 21-year-old woman with asthma and allergic rhinitis who had worsening symptoms and esophageal eosinophilia during the spring seasons with resolution in the winter season unrelated to diet.⁵

Further evidence for seasonality of EoE symptoms and esophageal eosinophilia has been described in other studies. Onbasi et al⁶ found that 26% of patients with allergic rhinitis without GERD had esophageal eosinophilia at biopsy examination during a time of active allergy symptoms. Wang et al⁷ found that significantly fewer cases of EoE were diagnosed in children during the winter season compared with spring, summer, and fall. They also reported that the severity of esophageal inflammation was less intense in the winter compared with the summer and fall. Similar results have been demonstrated with 330 cases of EoE reported in 4 additional studies, with an increase in the diagnosis of EoE during pollen seasons.^{8–11} Furthermore, in a series of 313 esophageal bolus impactions, Larsson et al¹² found an increase in impactions during summer and fall. However, Sorser et al¹³ evaluated 753 endoscopies in adults including 44 patients with EoE and did not find any seasonality to the diagnosis. Overall, there are 5 reports of seasonality of diagnosis and 3 reports of no seasonality.^{7–11,13–15}

In addition, 3 adults were recently reported to have developed EoE shortly after large allergen exposure to grass, mold, and dust.¹⁶ There also have been 2 interesting reports of adult patients developing EoE after starting sublingual immunotherapy (SLIT) for pollen and grass allergies; in these cases, EoE resolved with the cessation of SLIT.^{17,18} Furthermore, 1 pediatric patient had resolution of esophageal eosinophilia with a 2-year treatment of subcutaneous immunotherapy (SCIT) to dust mite.¹⁹ These cases further substantiate the potential relation between EoE and aeroallergens and suggest that in some patients aeroallergen sensitization underlies EoE in addition to the more common pattern of food allergen sensitization.

However, esophageal eosinophilia and EoE are used interchangeably when in fact esophageal eosinophilia is a histologic description signifying a variety of causes, such as, EoE, GERD, PPI-responsive esophageal eosinophilia, and quite possibly disease from aeroallergens.⁶

The authors examined the relation among esophageal eosinophilia, EoE, and aeroallergen sensitization or allergic rhinoconjunctivitis symptoms in 1,180 patients seen at the EoE clinic of the Children's Hospital of Philadelphia by analyzing demographics, evidence of aeroallergen sensitization, history or physical examination findings consistent with allergic rhinoconjunctivitis, and changes in esophageal eosinophil count in different seasons based on biopsy results in patients with confirmed EoE.

Methods

Patient Identification

The authors reviewed their database of the 1,180 patients diagnosed at the EoE clinic at the Children's Hospital of Philadelphia from January 1, 2006 through December 31, 2014 (Fig 1). All patients meet the standard definition of EoE.¹ The authors identified 160 patients with possible aeroallergen-induced EoE (AIEoE) based on 2 criteria: (1) patient-reported variation of EoE symptoms during pollen season and (2) changes in biopsy specimens during pollen season without changes in medication or diet. All patients were required to have at least 2 biopsy examinations. The authors also collected data regarding presence of atopic disease, including asthma, atopic dermatitis, allergic rhinoconjunctivitis, and IgE-mediated food allergy, self-identified sex and race, allergy skin

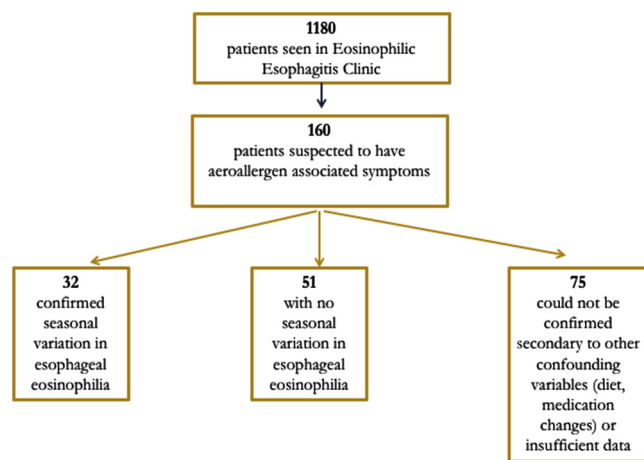


Figure 1. Enrollment flow chart. Charts for 1,180 patients seen at the Children's Hospital of Philadelphia Center for Pediatric Eosinophilic Disease were reviewed, and 146 patients had suspected aeroallergen-induced esophageal eosinophilia based on history. The distribution of these patients was based on biopsy findings from a retrospective chart review.

testing, ages at presentation and at various flares, and biopsy results from all endoscopies by chart review.

The study was approved by the institutional review board of the Children's Hospital of Philadelphia.

Disease Definitions

Eosinophilic esophagitis was defined as specific disease producing symptoms of esophageal dysfunction and more than 15 eos/hpf at esophageal biopsy examination while on appropriate therapy with a PPI for at least 2 months.¹ The authors have been pretreating with a PPI for at least 2 months before esophageal endoscopies since 2005. Esophageal eosinophilia was defined as the histologic presence of eosinophils in the esophagus from all causes. The 4 seasons were defined based on recent descriptions of pollen counts in the greater Philadelphia area.²⁰ Pollen seasons were defined as spring (March through May), summer (June through July) fall (August through October), and winter (November through February; eMethods). Biopsy-proved AIEoE was defined as changes in esophageal biopsy specimens from abnormal (<15 eos/hpf) to normal (>15 eos/hpf) and a 2-fold change in maximum eosinophil count during pollen season without changes in diet or medication.

In season was defined when a subject was symptomatic with EoE symptoms and had abnormal biopsy results. Out of season was defined when a subject was asymptomatic and normal biopsy results.

Standardized skin prick testing (SPT) was used (eMethods).²¹ Skin testing positively correlated with symptomatic season if tree sensitization occurred in patients with spring flares, grass sensitization in patients with summer flares, weed or ragweed sensitization in those with fall flares, and cat, dog, or dust mite sensitization in those with winter flares. Allergic rhinoconjunctivitis was diagnosed by a physician and confirmed based on history with physical examination findings consistent with allergic rhinoconjunctivitis and sensitization at SPT. The presence of asthma also was based on physician-confirmed diagnosis including the need for maintenance asthma therapy or recurrent wheezing responsive to albuterol. Children were diagnosed as allergic to food IgE if they developed immediate, classic symptoms with ingestion of a food described in the history and had been prescribed an epinephrine auto-injector. All patients had culprit food allergy confirmed by skin testing.²¹ Presence of food-induced EoE was defined as when a single food led to a change in esophageal biopsy specimens from normal (<15 eos/hpf) to abnormal (>15 eos/hpf).²

Statistical Analysis

Data were analyzed using GraphPad 6.0 (Prism Software, San Diego, California). All statistical tests were 2-tailed by using a .05 level of significance with the Fisher exact test or Student *t* test as needed. Data were expressed as mean $\pm$ SE unless otherwise stated.

Results

The authors noted that 1,180 patients seen in the Children's Hospital of Philadelphia Center for Pediatric Eosinophilic Disease were diagnosed with EoE using 2011 consensus guidelines.¹ These patients had 8,045 biopsy examinations and these were distributed throughout the year (eFig 1). Interestingly, there was a significant decrease in winter ($P < .05$) in the rate of positive esophageal biopsy results (eFig 2). However, the changes could have been due to changes in diet and/or medications. Therefore, the authors aimed to further clarify the role of aeroallergens in EoE. They identified patients who reported changes in their symptoms and changes in biopsy results without changes in diet or medication. One hundred sixty patients had suspected AIEoE based on patient-reported changes in esophageal symptoms and changes in esophageal biopsy results during pollen season without changes in diet or medication. Upon further chart review, 51 of these patients were found not to have seasonal change in esophageal eosinophilia and instead only showed histologic improvement with swallowed steroid therapy or dietary changes (typical therapy for EoE). Thirty-two patients had documented seasonal changes in esophageal eosinophilia at biopsy examination despite an unchanged diet and/or medication regimen and were considered to have biopsy-confirmed AIEoE. In the 32 patients with confirmed AIEoE, the maximal eosinophil count improved from 53.25 ± 4.6 eos/hpf during in-season biopsy examinations to 10.25 ± 1.67 during out-of-season biopsy examinations ($P < .0001$; Fig 2).

Of the 160 patients with suspected EoE, 75 patients appeared to have seasonal variation in their esophageal eosinophil counts at biopsy examination, but the authors were unable to confirm that these changes were due to seasonal aeroallergen exposure alone. These cases had concurrent dietary and medication changes or lacked follow-up biopsy examinations during relevant seasons.

Patient Characteristics

Of the 32 patients with AIEoE, the median age was 5 years at the time of initial EoE diagnosis (Table 1). Twenty-seven patients (84%)

Table 1

Demographics of all patients with EoE, those with EoE and suspected aeroallergen triggers, and those with EoE and biopsy-confirmed seasonal variation in esophageal eosinophilia

	Total EoE population	Biopsy-proved seasonal induced EoE	P value
n	1,180	32	
Median age (y)	5.2 ± 6.8	6.6 ± 5.11	.24
Boys	867 (73.5%)	27 (84%)	.17
Whites	956 (81%)	27 (84%)	.72
History of AR	865 (73%)	32 (100%)	.0007
History of asthma	721 (61%)	24 (75%)	.10
History of IgE-mediated FA	170 (15.7%)	13 (41%)	.002
Food-induced EoE	1156 (98%)	22 (69%)	.0001

Abbreviations: AR, allergic rhinitis; EoE, eosinophilic esophagitis; FA, food allergy.

were boys, reflecting a similar percentage in the total EoE cohort (74%). Of the 32 patients with aeroallergen-associated symptoms, all (100%) had a history or physical examination consistent with allergic rhinitis. The presence of asthma and IgE-mediated food allergy was higher in this subset of patients compared with the full EoE cohort (75% vs 61% and 41% vs 15.7% respectively, $P = .10$ for asthma and .002 for IgE-mediated food allergy). Twenty-two (69%) of the AIEoE cohort also had evidence of food-induced symptoms and changes in esophageal eosinophilia owing to food removal or addition. This is significantly lower than in the overall EoE cohort, which reflects that 98% of patients had some history or clinical findings suggestive of food-induced EoE.

Seasonality

There were 40 flares documented in the group of 32 patients with seasonal triggers. Twenty-five patients demonstrated the involvement of a single season. The most common season involved for these patients was spring ($n = 14$), followed by summer ($n = 12$). Fewer flares were observed in fall ($n = 7$) and winter ($n = 7$; Fig 3). Seven patients had exacerbations in 2 different seasons. Two of these patients had exacerbations in the spring and summer, 2 patients in the spring and fall, 1 patient in the summer and fall, 1 patient in the spring and winter, and 1 patient in the fall and winter.

Of the 32 patients with confirmed AIEoE, 17 had relevant skin testing results available for review (Fig 4). Two patients had negative results to all aeroallergens tested. Of the remaining 15 with relevant positive skin test results, 15 patients (87% of total group with available relevant testing results) had evidence of

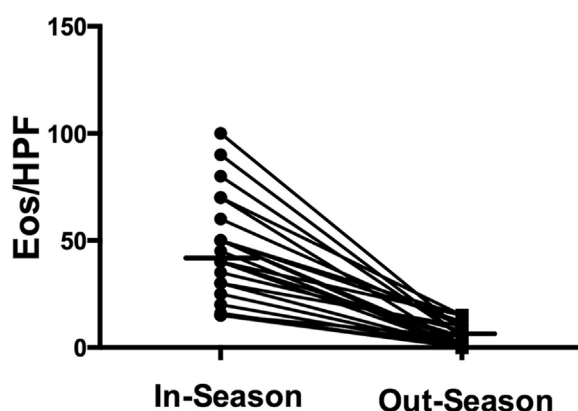


Figure 2. In-season vs off-season esophageal eosinophilia. Esophageal eosinophilia increased significantly in patients with a positive biopsy result during their pollen season (in-season) compared with no symptoms without changes in diet or medication (off-season; $P < .0001$). Each point represents maximal esophageal eosinophilia expressed as eosinophils per high-power field (Eos/HPF) during the symptomatic vs asymptomatic season. The mean eosinophilia count is indicated.

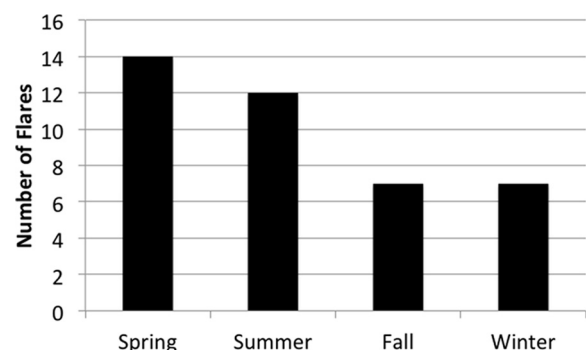


Figure 3. Seasonality of esophageal eosinophilia. The number of season flares was defined as changes in esophageal eosinophilia from fewer than to more than 15 eosinophils per high-power field and doubling of baseline esophageal eosinophilia without changes in diet or medications. Percentages are expressed as the percentage of the total number of flares.

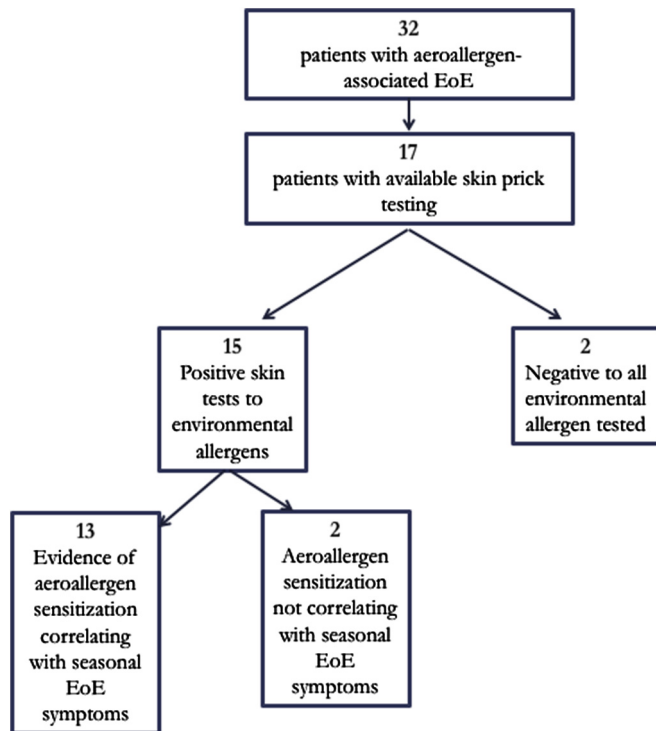


Figure 4. Correlation of aeroallergen sensitization with seasonality of aeroallergen-induced eosinophilic esophagitis (EoE) flares. Skin prick testing results from 32 patients with aeroallergen-triggered EoE were reviewed. Seventeen patients had skin prick testing results available. Thirteen patients (76%) demonstrated sensitization to aeroallergens that correlated with their EoE symptoms.

sensitization to an aeroallergen that correlated with their seasonal variation of EoE, whereas 2 patients (13% of total group with available relevant testing results) had sensitization to allergens that did not correlate with their symptomatic season. Fifty percent of patients also had sensitization to allergens outside the AIEoE season.

Discussion

Of the 1,180 patients diagnosed with EoE, 160 (14%) were initially suspected of having aeroallergen-associated triggers. Of these 160 patients, 32 (3% of the total) had biopsy-confirmed variation of esophageal eosinophilia triggered by aeroallergens and were considered to have AIEoE. Most patients were boys (84%), all had a history or examination consistent with allergic rhinitis, and most had a history of asthma (75%). All 32 patients had clear seasonal variation, with change from normal to more than 15 eos/hpf and at least a 2 times increase in their esophageal eosinophilia during their on-peak seasons. Of those with seasonal variation, most biopsy-confirmed flares occurred during the spring, followed closely by summer. Consistent with the role of seasonal induced symptoms, multiple flares were documented in the same seasons in 5 patients in different years (data not shown). Fewer flares occurred during the fall and winter. Fifty-one patients initially suspected of having a “seasonal flare” of EoE in fact demonstrated no esophageal histologic change at biopsy review.

The presence of AIEoE could not be confirmed in 75 patients because of concurrent changes in diet and/or medications or a lack of a follow-up biopsy result. If all 75 patients did in fact have esophageal variation consistent with seasonal triggers, then AIEoE would be seen in 9% of the full EoE cohort. It is more likely that a smaller percentage of these patients would have confirmatory biopsy results to meet the criteria for AIEoE.

Interestingly, although the presence of IgE-mediated food allergy was much higher in the AIEoE cohort, the presence of food-triggered EoE was significantly lower. This noteworthy difference might be an indication of the different pathophysiology that could be involved in the subset of patients who have AIEoE. Although classic EoE seems to be driven by food allergens, this subset could have different mechanisms similar to what Mishra et al⁴ described, in which patients are sensitized by intranasal exposure and subsequent delivery of allergen to the esophagus. Previous work by Sugnanam et al²² demonstrated a switch to more pollen sensitization in adults compared with foods in children starting as young as 4 years. This is in line with previous studies examining the question of seasonality of EoE in adults; all these studies did indeed find seasonal variation in EoE in adults.^{6,8–10} In contrast, the pediatric studies have not as consistently shown seasonal variation, and the few studies that have not shown seasonality were performed in children.^{7,9,11,13–15} These observations support the idea that aeroallergen sensitization might be more relevant for EoE in adults than in children.

Similar to previous studies,^{7,9,10,12} the present data confirmed that more patients experienced seasonal changes in esophageal eosinophilia in the spring and summer compared with the fall and winter. Of 17 patients with available SPT results, most (71%) had seasonal flares that correlated with SPT results. Four patients had flares in seasons that did not correlate to SPT results: 2 had negative SPT results to all major aeroallergens and 2 had negative SPT results to most major aeroallergens. The patients with non-correlating flares were younger on average compared with the group with correlating flares (mean age 3.75 vs 10.2 years, $P = .04$). A possible explanation for this is that aeroallergen SPT results can often be negative in young children with allergic rhinitis but become positive later in life. These children also might be more of an entopic phenotype, in which patients have localized allergic sensitization that is not detected at allergy testing. Winter-associated allergic rhinoconjunctivitis is likely secondary to increased exposure to perennial allergens, including indoor pets and dust mite. Although some patients with winter flares had no SPT data available, all but 1 of those with SPT data had evidence of dust mite or pet sensitization. Fifty percent of patients also were sensitized to other allergens that did not cause changes in EoE biopsy results. There are several potential reasons for this observation, including biopsy specimens not taken during the appropriate pollen season or food or medication biopsy examinations performed at the same time, so changes could not be identified. Patients were more sensitized or more EoE sensitized to one pollen than another and SPT does not identify this difference in sensitivity. The pollen season was too mild to induce symptoms.

In the present cohort of 32 patients with AIEoE, 22 also had typical food-induced esophageal eosinophilia at biopsy examination with resolution of histologic abnormalities and symptoms owing to modifications in the diet (typical of EoE). These patients had at least 2 reasons to have esophageal eosinophilia, including EoE and AIEoE.

In accordance with the concept that swallowing aeroallergens can cause EoE, 2 case reports of SLIT leading to EoE have been described.^{17,18} Although SLIT might cause EoE symptoms in some patients because of sensitization through the oropharynx and gastrointestinal tract, SCIT against pertinent aeroallergens might be an important and powerful tool in managing this subset of patients with clear aeroallergen-triggered symptoms consistent with AIEoE. Consistent with this theory, 1 patient had resolution of her EoE with 2-year treatment of SCIT for dust mite.¹⁹

The present study represents the largest cohort of pediatric patients to have biopsy-confirmed seasonal variation in their EoE. Although food-induced EoE is by far the most common cause of severe esophageal eosinophilia in patients treated with PPIs (close

to 95%), the present data support the hypothesis that aeroallergens can be a trigger for esophageal eosinophilia in a small subset of patients. AIEoE also can cause a “secondary” esophageal eosinophilia in patients who also have food-induced EoE.

Eosinophilic esophagitis is a difficult disease to diagnose and treat. Historically, EoE has been treated with drastic dietary modifications that often lead to extremely poor quality of life or oral steroids that can have deleterious effects in the long term that have yet to be studied extensively. Over the years, many investigators have described several different mechanisms that could be at play in a subset of patients who clearly have seasonal variation in their EoE symptoms. The present study shows that identifying food triggers alone might not be sufficient in select patients. Aggressively identifying and treating allergic rhinoconjunctivitis in patients with EoE could alleviate symptoms in these patients, and there might be a role for immunotherapy against targeted aeroallergens as an effective method of controlling eosinophilia in this disease.

For the diagnosis of esophageal eosinophilia, the present data suggest the addition AIEoE to the current differential diagnosis of EoE, GERD, PPI-responsive esophageal eosinophilia, and eosinophilic gastroenteritis. Further prospective clinical studies are needed to fully characterize this subset of patients with EoE. Also, additional studies are needed to identify different mechanistic pathways within this disease process.

Supplementary Data

Supplementary data related to this article can be found online at <http://dx.doi.org/10.1016/j.anai.2015.07.004>.

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eMethods

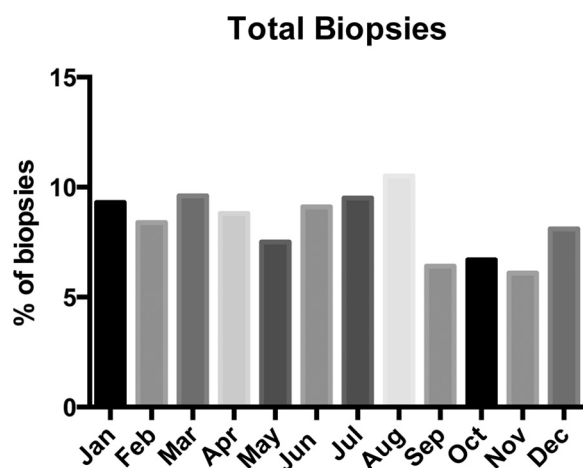
Pollen Seasons

Seasons were based on pollen seasons in the local Philadelphia area: spring, March through May; summer, June through July; fall, August through October; and winter, November through February.

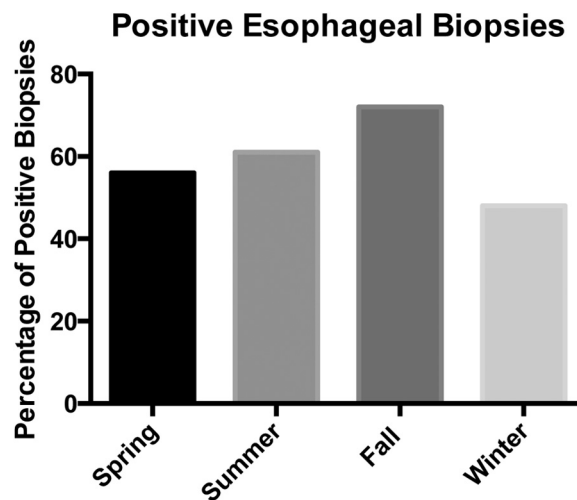
Skin Testing

Briefly, SPT was performed using a commercial extract (Greer Laboratories Inc, Lenoir, North Carolina) and applied on the forearm

with a bifurcated needle (Allergy Labs of Ohio Inc, Columbus, Ohio) by pricking through a drop of the extract, which was then absorbed. Reactions were recorded by measuring the largest diameter of the wheal and flare in millimeters at 15 minutes. The test result was considered positive if the wheal was 3 mm larger than the negative control.



eFigure 1. Total esophageal biopsy results for eosinophilic esophagitis per month of biopsy specimens obtained expressed as the percentage of total biopsies (8,045).



eFigure 2. Positive esophageal biopsy results were defined as more than 15 eosinophils per high-power field regardless of treatment. Percentages are expressed as the total number of positive biopsy results divided by the total number of biopsy specimens obtained during the period. Spring, March through June; summer, July through August; fall, September through November; winter, December through February.