



What Is the Relationship Between Eosinophilic Esophagitis (EoE) and Aeroallergens? Implications for Allergen Immunotherapy

Maureen Egan^{1,2} · Dan Atkins^{1,2}

© Springer Science+Business Media, LLC, part of Springer Nature 2018

Abstract

Purpose of Review Observations suggesting that aeroallergens trigger eosinophilic esophagitis (EoE) in a subset of patients raise questions about the implications this finding has on the evaluation and management of patients with EoE, including a potential role for allergen immunotherapy.

Recent Findings The majority of studies evaluating the potential role of aeroallergens as provocateurs of EoE have addressed this issue by assessing the seasonal variation in EoE diagnosis and/or symptom onset or worsening, with mixed results. For various reasons, reaching accurate conclusions based on this methodology is potentially fraught with error. In addition, studies examining the even harder to assess role of perennial aeroallergens in triggering EoE are lacking. Although clearly not the majority, there may be a subset of patients with EoE and allergic rhinitis in whom exposure to aeroallergens to which they are sensitized contributes to esophageal eosinophilia either through direct chronic esophageal mucosal contact with pollen allergens or from repetitive exposure of the esophageal mucosa to pollen allergens, mediators, and eosinophils in swallowed nasal secretions. Therefore, evaluation for and optimal treatment of comorbid allergic rhinitis in EoE patients are clearly indicated. Recognition of the potential role of aeroallergens as triggers of EoE also raises the question of whether allergen immunotherapy might be an effective form of EoE treatment. Reports of sublingual immunotherapy (SLIT) inducing EoE support the notion that aeroallergens can trigger EoE, but negate this approach as a potential form of EoE therapy. In fact, the use of SLIT is contraindicated in patients with EoE. The literature regarding the role of subcutaneous immunotherapy (SCIT) in patients with EoE is limited. Current evidence indicates that it should not be typically recommended; however, SCIT might benefit a subset of patients with EoE and uncontrolled allergic rhinitis on conventional therapies in whom SCIT would otherwise be indicated for allergic rhinoconjunctivitis, particularly in those with sensitizations to pollens containing allergens that cross react with food allergens.

Summary The purpose of this review is to discuss the current literature examining the role of aeroallergens in triggering EoE with a focus on the potential clinical implications of this finding on managing patients with EoE.

Keywords Eosinophilic esophagitis · Allergic rhinitis · Subcutaneous immunotherapy · Sublingual immunotherapy

Introduction

Initially described in the early 1990s, eosinophilic esophagitis (EoE) has since increased in prevalence worldwide to a current estimate of approximately 1 in 2000, becoming one of the most commonly identified conditions in infants and children with feeding issues and adolescents and adults presenting with dysphagia or food impaction [1–3]. For example, in a study of 548 patients presenting with esophageal foreign body impactions, 9% were found to have EoE and having EoE was identified as the strongest predictor of multiple food impactions [4]. Initial consensus recommendations for diagnosis and treatment of EoE published first in 2007 and updated in 2011 defined EoE as a chronic, antigen-mediated esophageal

This article is part of the Topical Collection on *Immunotherapy and Immunomodulators*

✉ Dan Atkins
Dan.Atkins@childrenscolorado.org

Maureen Egan
maureen.egan@childrenscolorado.org

¹ Section of Allergy and Immunology, Department of Pediatrics, Children's Hospital of Colorado, 13123 East 16th Ave, Box 518, Aurora, CO 80045, USA

² Gastrointestinal Eosinophilic Disease Program, University of Colorado School of Medicine, 13123 East 16th Ave, B290, Aurora, CO 80045, USA

disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation [5, 6]. Although for years the diagnosis of EoE was reserved only for patients whose esophageal eosinophilia persisted after a proton pump inhibitor (PPI) trial, recent recommendations propose dropping the lack of a PPI response as a diagnostic criterion and considering PPIs as an effective form of therapy for some patients [7, 8].

Recognizing the central role of chronic antigen exposure in the pathogenesis of EoE emphasizes the importance of accurately identifying all potential triggers for each patient. The major function of the esophagus is to serve as a conduit for moving food from the oropharynx to the stomach. During the performance of this task, the esophageal mucosa is repeatedly exposed to large amounts of numerous food antigens. Thus, it stands to reason that food antigens have been identified as the most common triggers of EoE in studies documenting the resolution of symptoms and esophageal mucosal eosinophilic inflammation within weeks of adhering to various types of elimination diets [6]. As would be expected, given the associated lack of exposure to intact food antigens, the use of elemental diets is most effective with resolution rates exceeding 90% [9]. However, success with less onerous empiric diets eliminating either the six (SFEDs) or four (FFEDs) most common food allergens or targeted elimination diets developed based on the identification of food antigen triggers through the use of skin prick testing (SPT) and atopy patch testing (APT) is significant, approaching 75% [10]. Return of culprit foods to the diet has been shown to result in a relatively rapid recurrence of symptoms and histological findings, confirming these foods as the disease trigger. Milk is the most commonly identified culprit food followed by egg, wheat, and soy in children in the USA, with milk and wheat the most common triggers in adults [11]. It has been estimated that a single food triggers disease in between 30 and 50% of EoE patients with only two foods triggering disease in about another third, and the remainder triggered by more than two foods [12]. Given the vast number of food antigens to which the esophagus is regularly exposed, it is fascinating that in many patients such a small number of the same foods are repeatedly implicated as the trigger, raising questions about which characteristics of these foods and their exposure patterns make them a common trigger.

Although the majority of patients respond to food elimination diets, the lack of an adequate response to dietary changes in a portion of EoE patients implies that antigens other than food allergens can play a role [9, 13]. Several lines of evidence suggest that aeroallergens are capable of triggering EoE. Early murine models of EoE were induced by initial sensitization followed by intranasal challenges of sensitized mice with the corresponding aeroallergen such as *Aspergillus fumigatus*, dust mite, or cockroach [13]. In addition, many patients with EoE have documented allergic rhinitis and/or asthma with

sensitization to environmental inhalant allergens demonstrated by positive SPTs and an associated increase in allergic ocular, nasal, and/or chest symptoms during the corresponding pollen season. Sensitization to environmental aeroallergens was documented in 79% of one pediatric cohort, and overall, SPT of children with EoE has demonstrated increasing sensitization to inhalant allergens accompanied by a decrease in food allergen sensitivity with aging, as would be predicted by the atopic march [14, 15]. Although exposure of the esophageal mucosa to aeroallergen antigens is miniscule when compared to the amount of food antigen exposure, the ubiquitous nature of aeroallergens makes complete avoidance difficult. The correlation between EoE disease activity and seasonal aeroallergen exposure was clearly documented in a case report by Fogg et al. with repeated endoscopies in an adult patient who experienced spontaneous disease remission and a return of disease correlating with the pollen season [16]. In addition, an initial report of high sensitization to profilins and PR-10 in patients with EoE combined with a report showing that adults with EoE have a high prevalence of pollen food allergy syndrome (PFAS) and pollen sensitization further supports a potential role for aeroallergens in the pathogenesis of EoE and suggests that eating foods that contain allergens that cross react with pollen allergens might also drive disease [17]. A review of the literature reveals several reports that support a role for aeroallergens while other studies refute this assertion. These reports will be reviewed in the following sections.

Studies Supporting a Relationship Between Eosinophilic Esophagitis and Aeroallergens

As previously mentioned, the first study to suggest a relationship between aeroallergens and EoE was by Mishra et al. who noted the development of esophageal eosinophilia after intranasal exposure to *Aspergillus fumigatus* in a murine model [18•]. The authors suggested that intranasal exposure to aeroallergen leads to topical delivery of the allergens to the esophagus and subsequent development of EoE [18•]. Further studies in humans have also noted increased eosinophils in the esophagus of patients with allergic rhinitis during the pollen season [16, 19]. Specifically, Onbasi et al. sought to determine whether there was evidence of eosinophil recruitment to the esophagus in adult patients with seasonal allergic rhinitis [19]. Thirty-eight patients with symptomatic allergic rhinitis who were sensitized to grass pollen and had endoscopies done during the grass pollen season were included, in addition to 25 non-atopic controls and 24 patients with gastroesophageal reflux disease (GERD). They noted esophageal eosinophilia with a mean number of 5.5 eosinophils per high powered field in 26% of the allergic rhinitis patients, in 21% of those with GERD and in none of the non-atopic controls [19]. While the

degree of esophageal eosinophilia noted in those with allergic rhinitis did not meet diagnostic criteria for EoE [7•], it raises the question of whether allergic rhinitis and subsequent topical delivery of aeroallergens to the esophagus contribute to esophageal eosinophilia in sensitive patients with EoE. This is pertinent, as patients with EoE often have concomitant atopic disease, including allergic rhinitis, as described above [7•].

Most studies that have specifically evaluated the potential role of aeroallergens in patients with EoE have addressed this issue by assessing the seasonal variation in EoE diagnosis and/or symptom onset, with mixed results amongst the literature. Wang et al. performed a retrospective analysis of children diagnosed with EoE over a 6-year period and noted that significantly fewer were diagnosed in the winter when compared to the spring [20]. Similarly, Fahey et al. performed a retrospective chart review of pediatric patients diagnosed with EoE at an academic hospital in New York City and compared onset of symptoms and histological diagnosis to local pollen counts [21]. They noted a seasonal variation in both onset of symptoms and diagnosis, with the highest number of patients reporting symptoms from July to September and diagnosis from October to December, which they attributed to symptom onset corresponding with peak grass pollen levels. However, of the 11 taxa examined at each pollen center, there was only a correlation found between grass pollen and EoE [21]. Additionally, Moawad et al. correlated mean pollen counts for trees, grasses, and weeds with EoE diagnoses in adult patients and noted a significant association between diagnosis and grass pollen prevalence, but not tree or weed pollen counts [22]. Prasad et al. noted an increased prevalence of EoE diagnosis in the late summer/fall which paralleled the increase in endoscopy volume [23]. Almansa et al. performed a retrospective review on adult cases newly diagnosed with EoE over the course of 1 year, and of the 41 patients diagnosed, there was a significant increase in number of diagnoses in the spring and summer compared to the fall, which was stable when compared to the total number of endoscopies performed [24]. In order to conclude that aeroallergens are causal in EoE, one might expect patients would be sensitized to aeroallergens and have clinically apparent allergic rhinitis, which was not the case for most participants in the previously mentioned studies. More specifically, only 4 of the 234 participants in the Wang et al. cohort were noted to have rhinitis [20], as were only 38% of participants in the study by Fahey et al. [21] and 24.4% of the cohort described by Almansa et al. [24]. Alternatively, if as noted with food triggers, immediate allergic symptoms on exposure are not observed, and skin tests are often negative, identifying the causative allergen and proving the association between aeroallergen exposure and EoE becomes even more difficult.

Studies that report worsening of EoE during the pollen season are adding further support for a role of aeroallergens in triggering EoE [25•, 26, 27]. Specifically, Larsson et al.

noted an increase in food impactions during the summer and fall [26]. Wolf et al. reported on three adult patients who developed EoE shortly after large allergen exposures to grass, mold, and dust mite [27]. However, follow-up information on these patients is lacking, making it difficult to prove causality. A role for topical exposure of the esophagus to aeroallergens leading to the development of EoE is also supported by cases of EoE induced by sublingual immunotherapy (SLIT) with resolution upon discontinuation [28, 29]. In fact, package inserts for currently available SLIT products in the USA list EoE as a contraindication of use [30].

In perhaps the best designed study thus far evaluating the role of aeroallergens in EoE, Ram et al. performed a retrospective chart review to determine the incidence of patients with seasonal-induced esophageal eosinophilia amongst pediatric patients with known eosinophilic esophagitis. Seasonal-induced eosinophilia was defined as a change from remission of EoE (< 15 eos/hpf) with a minimum twofold increase in eosinophil counts between two consecutive biopsy specimens in different seasons without dietary or medication modifications [25•]. Of the 1180 patients with EoE included, 14% were suspected to have aeroallergen-associated triggers of EoE based on history, of which 20% (32 patients total) had biopsy confirmed variation of esophageal eosinophilia triggered by aeroallergen, all of whom had allergic rhinitis [25•]. These findings demonstrate that there may be a subset of patients with EoE and allergic rhinitis in whom aeroallergen exposure may contribute to flares of EoE.

Studies Refuting a Relationship Between Eosinophilic Esophagitis and Aeroallergens

There have been similarly designed studies that assessed for seasonal variation in diagnosis and/or onset of clinical symptoms of eosinophilic esophagitis that did not note a relationship [31–34]. Sorser et al. reviewed all esophageal biopsies performed on patients less than 21 years of age between 2001 and 2006 at their institution, and amongst 763 performed, 44 (5.8%) of which were patients with EoE, no seasonal correlation was noted [32]. They similarly noted an absence of correlation between onset of symptoms and seasons [32]. Schlegel et al. evaluated the relationship between EoE diagnosis in pediatric patients and pollen and mold counts and found that there was no association. In addition, the proportion of EoE diagnoses was evenly distributed compared to the total number of biopsies performed without seasonal variation [33]. Kagawalla et al. recruited 78 pediatric participants across four medical centers for evaluation of the four-food elimination diet, which required frequent endoscopies at roughly 8-week intervals and noted no seasonal influence in responders versus non-responders, with more responders having post-treatment

endoscopies performed during the pollen season than non-responders (not statistically significant) [35]. In other pediatric populations, Elitsur et al. evaluated for seasonal trends in 95 patients diagnosed with EoE living in rural communities and noted that rates of diagnosis were similar in all seasons [34]. Other studies have similarly noted a lack of seasonal variation in the diagnoses of EoE [31, 34].

Given the heterogeneity in studies, particularly in regard to age of patients and geographic location which would impact pollen profiles, Lucendo et al. performed a systematic review to determine the relationship between seasonal variation and clinical symptoms, specifically food bolus impaction, and diagnosis of EoE [36]. Eighteen studies involving 16,846 patients were included, and 27.1% of cases were diagnosed in the spring compared to 22.1% in the winter, with no statistical differences noted in either EoE diagnoses or food bolus impaction and seasonal variation [36].

Critical Appraisal of the Literature

Overall, most studies evaluating the role of aeroallergens in EoE have primarily searched for a seasonal variation in symptom onset and/or diagnosis. There are inherent difficulties in making firm conclusions based on this approach, as many patients with EoE have a diagnostic delay of varied amounts of time. Additionally, given that most patients with EoE are atopic, symptoms suggestive of EoE may be elicited during allergy visits primarily for other allergic disorders scheduled during the pollen season [37]. It is also difficult to conclude that the prevalence of food impaction directly correlates with seasonal variation of EoE, as eating customs may differ seasonally with outdoor barbecues in the summer, for example, making a bolus impaction more likely [37]. Regional variability in the timing and types of aeroallergen exposures, in addition to annual differences pollen yields might also confound the impact of aeroallergen exposure on patients with EoE.

Additionally, the absence of studies that evaluate for the role of perennial aeroallergens in relationship to EoE is problematic. Given that these exposures are year-round and the allergens are often prevalent in the patient's home, accurate assessment is difficult. Continuous exposure would be predicted to lead to persistent symptoms that would be harder to associate with perennial aeroallergen exposure than the seasonal worsening reported in association with seasonal aeroallergen exposure. However, if seasonal aeroallergens were truly a prominent inciting or exacerbating factor in EoE, one would assume that this would also be the case with perennial allergens. Therefore, there would be a significant portion of patients with perennial aeroallergen sensitizations who were refractory to current EoE therapies such as elimination diets, which does not appear to be the case [6, 7]. Also, as

suggested by responses to elimination diets, there may be only a minority of patients in whom aeroallergen exposure truly plays a significant role. Aeroallergens may also be only a minor provocateur in some patients or only cause worsening when the esophageal mucosa is inflamed from exposure to more prominent triggers such as food allergens.

Implications for Evaluation and Management Including Immunotherapy

The weight of evidence provided by clinical experiences and a review of the somewhat conflicting literature suggest that aeroallergen exposure plays a substantial role in a minority of patients and at least a partial role in others in triggering EoE. Knowledge of this fact and realizing that chronic exposure of the esophageal mucosa to antigen is the driving force of the eosinophilic inflammation that defines EoE underscore the importance of identifying all potential triggers for each EoE patient and thoroughly evaluating and optimally controlling comorbid allergic disease. An example of lessons to be learned from this approach is illustrated by a study by Pesek et al. who found that children with EoE with perennial allergen and mold sensitization were more likely to fail combination diet and swallowed corticosteroid treatment [38]. Thus, obtaining a thorough history to identify the presence and timing of comorbid allergic diseases and skin testing to aeroallergens is warranted, followed by monitoring to determine whether flaring of EoE or other allergic disease correlates with exposure to allergens to which the patient is sensitized. These findings have practical implications involving care such as, for one example, determining the optimal timing of endoscopies. Thorough education regarding allergen avoidance measures and closer monitoring while also providing optimal treatment including the use of topical nasal steroid preparations during corresponding allergen seasons or unavoidable allergen exposures is advised.

Although elimination diets or/and swallowed topical steroids with dilation as required are the therapies that first come to mind for EoE, aeroallergen involvement raises the question of whether allergen immunotherapy could be of benefit. Sublingual (SLIT) or oral (OIT) routes of immunotherapy are currently contraindicated in patients with known EoE due to reports of the development of EoE in a small portion of patients on these therapies with resolution of disease after discontinuation [28, 29, 39]. In fact, these reports emphasize the importance of monitoring all patients on SLIT or OIT for the onset of symptoms suggestive of evolving EoE. Alternatively, several lines of evidence point to a potential role for considering subcutaneous allergen immunotherapy (SCIT) as a potential treatment for a subset of EoE patients worthy of further investigation. Van Rhijn et al. [40] and Simon et al.

[41] showed increased sensitization to profilins and PR-10 in EoE patients. In addition, a high prevalence of PFAS in adults with EoE was reported by Mahdavi et al. [17], while a recent case report described a child with EoE linked to PFAS [42]. However, current evidence for using SCIT in EoE is limited to case studies [43]. Furthermore, while topical antigen delivery to the esophagus is thought to be the primary mechanism of exposure in EoE, it is possible that systemic exposure of antigens may also contribute. For example, inflammation can be seen in children receiving food allergens via gastrostomy tube. Therefore, it is possible that systemic exposure of aeroallergens via SCIT may exacerbate EoE. This has been demonstrated in a case report of a child with severe grass allergy and well-controlled EoE who demonstrated recurrence of EoE while on SCIT [44]. Given this theoretical risk, it would be reasonable, in the authors' opinion, to pursue SCIT only after the patient's EoE is well controlled.

The use of SCIT in any EoE patient based on positive skin tests to aeroallergens alone cannot be recommended as, has also been observed with skin testing to foods, many EoE patients are sensitized to allergens that do not appear to drive disease. Thus, reserving SCIT only for those patients who meet criteria for treatment of allergic rhinitis and preferably those who also report symptoms suggestive of PFAS seems reasonable at this point. An initial increase in symptoms might be encountered in some patients in the initial stages of SCIT, and patients should be informed that significant evidence that SCIT will result in improvement in or resolution of EoE is currently lacking. Obviously, though somewhat difficult to address, this is an area that would greatly benefit from future well-designed studies. More specifically, randomized placebo-controlled trials are needed which examine the safety and efficacy between SCIT and conventional therapy for AR amongst patients with EoE who have clear seasonal exacerbations and aeroallergen sensitization.

Conclusions

Based on the current literature, it appears that aeroallergens might play a prominent role in only a minority of patients with EoE. However, it has previously been suggested that different phenotypes exist for EoE, similar to asthma and inflammatory bowel disease [45], indicating that there may be a subset of patients with EoE in whom aeroallergen exposure is more relevant, as demonstrated by Ram et al. [25]. Therefore, evaluation for and judicious treatment of comorbid allergic rhinitis are essential and potentially beneficial. SLIT for treatment of allergic rhinitis in patients with EoE should be avoided [30]. Future studies are needed to better evaluate the role of SCIT in patients with EoE. It would be reasonable to recommend SCIT in EoE patients

who would otherwise be an appropriate SCIT candidate for management of their allergic rhinitis. The authors recommend that SCIT only be initiated after the patient is on appropriate treatment and their EoE is well controlled. However, in the absence of allergic rhinitis not controlled on conventional therapies, the literature currently does not support a role for SCIT in the treatment of EoE.

Funding Sources Both M.E. and D.A. have funding from Consortium for Gastrointestinal Eosinophilic Research (CEGIR). CEGIR (U54 AI117804) is part of the Rare Diseases Clinical Research Network (RDCRN), an initiative of the Office of Rare Diseases Research (ORDR), NCATS, and is funded through collaboration between NIAID, NIDDK, and NCATS and patient advocacy groups including APFED, CURED, and EFC.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Attwood SE, Smyrk TC, Demeester TR, Jones JB. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci*. 1993;38(1):109–16.
2. Straumann A, Spichtin HP, Bernoulli R, Loosli J, Vogtlin J. Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings. *Schweiz Med Wochenschr*. 1994;124(33):1419–29.
3. Mansoor E, Cooper GS. The 2010–2015 prevalence of eosinophilic esophagitis in the USA: a population-based study. *Dig Dis Sci*. 2016;61(10):2928–34.
4. Sperry SL, Crockett SD, Miller CB, Shaheen NJ, Dellon ES. Esophageal foreign-body impactions: epidemiology, time trends, and the impact of the increasing prevalence of eosinophilic esophagitis. *Gastrointest Endosc*. 2011;74(5):985–91.
5. Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology*. 2007;133(4):1342–63.
6. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011;128(1):3–20.e6. quiz 1–2.
7. Lucendo AJ, Molina-Infante J, Arias A, von Arnim U, Bredenoord AJ, Bussmann C, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United European Gastroenterol J*. 2017;5(3):335–58. **Updated guidelines on**

eosinophilic esophagitis which highlight the potential role of proton pump inhibitors for treatment of EoE.

8. Molina-Infante J, Gonzalez-Cordero PL, Lucendo AJ. Proton pump inhibitor-responsive esophageal eosinophilia: still a valid diagnosis? *Curr Opin Gastroenterol*. 2017;33(4):285–92.
9. Arias A, Gonzalez-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology*. 2014;146(7):1639–48.
10. Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol*. 2012;130(2):461–7.e5.
11. Greenhawt M, Aceves SS, Spergel JM, Rothenberg ME. The management of eosinophilic esophagitis. *J Allergy Clin Immunol Pract*. 2013;1(4):332–40. quiz 41–2.
12. Spergel JM AS. Allergic components of eosinophilic esophagitis. *J Allergy Clin Immunol*. 2018. 2018; In press.
13. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology*. 1995;109(5):1503–12.
14. Assa'ad AH, Putnam PE, Collins MH, Akers RM, Jameson SC, Kirby CL, et al. Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. *J Allergy Clin Immunol*. 2007;119(3):731–8.
15. Sugnanam KK, Collins JT, Smith PK, Connor F, Lewindon P, Cleghorn G, et al. Dichotomy of food and inhalant allergen sensitization in eosinophilic esophagitis. *Allergy*. 2007;62(11):1257–60.
16. Fogg MI, Ruchelli E, Spergel JM. Pollen and eosinophilic esophagitis. *J Allergy Clin Immunol*. 2003;112(4):796–7.
17. Mahdavinia M, Bishehsari F, Hayat W, Elhassan A, Tobin MC, Ditto AM. Association of eosinophilic esophagitis and food pollen allergy syndrome. *Ann Allergy Asthma Immunol*. 2017;118(1):116–7.
18. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest*. 2001;107(1):83–90. **The first study which demonstrates a role of aeroallergens in EoE by demonstrating esophageal eosinophilia following intranasal exposure in a mouse model.**
19. Onbasi K, Sin AZ, Doganavsargil B, Onder GF, Bor S, Sebik F. Eosinophil infiltration of the oesophageal mucosa in patients with pollen allergy during the season. *Clin Exp Allergy*. 2005;35(11):1423–31.
20. Wang FY, Gupta SK, Fitzgerald JF. Is there a seasonal variation in the incidence or intensity of allergic eosinophilic esophagitis in newly diagnosed children? *J Clin Gastroenterol*. 2007;41(5):451–3.
21. Fahey L, Robinson G, Weinberger K, Giambrone AE, Solomon AB. Correlation between aeroallergen levels and new diagnosis of eosinophilic esophagitis in New York City. *J Pediatr Gastroenterol Nutr*. 2017;64(1):22–5.
22. Moawad FJ, Veerappan GR, Lake JM, Maydonovitch CL, Haymore BR, Kosisky SE, et al. Correlation between eosinophilic oesophagitis and aeroallergens. *Aliment Pharmacol Ther*. 2010;31(4):509–15.
23. Prasad GA, Alexander JA, Schleck CD, Zinsmeister AR, Smyrk TC, Elias RM, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. *Clin Gastroenterol Hepatol*. 2009;7(10):1055–61.
24. Almansa C, Krishna M, Buchner AM, Ghabril MS, Talley N, DeVault KR, et al. Seasonal distribution in newly diagnosed cases of eosinophilic esophagitis in adults. *Am J Gastroenterol*. 2009;104(4):828–33.
25. Ram G, Lee J, Ott M, Brown-Whitehorn TF, Cianferoni A, Shuker M, et al. Seasonal exacerbation of esophageal eosinophilia in children with eosinophilic esophagitis and allergic rhinitis. *Ann Allergy Asthma Immunol*. 2015;115(3):224–8.e1. **Retrospective chart review to determine the incidence of seasonal-induced esophageal eosinophilia in pediatric EoE patients which demonstrated its presence in a small subset of patients.**
26. Larsson H, Bergquist H, Bove M. The incidence of esophageal bolus impaction: is there a seasonal variation? *Otolaryngol Head Neck Surg*. 2011;144(2):186–90.
27. Wolf WA, Jerath MR, Dellon ES. De-novo onset of eosinophilic esophagitis after large volume allergen exposures. *J Gastrointest Liver Dis*. 2013;22(2):205–8.
28. Antico A, Fante R. Esophageal hypereosinophilia induced by grass sublingual immunotherapy. *J Allergy Clin Immunol*. 2014;133(5):1482–4.
29. Miehlke S, Alpan O, Schroder S, Straumann A. Induction of eosinophilic esophagitis by sublingual pollen immunotherapy. *Case Rep Gastroenterol*. 2013;7(3):363–8.
30. Available from: www.fda.gov/food/guidanceRegulation/GuidanceDocumentsRegulatoryInformation/Allergens/ucm106890.htm.
31. Frederickson NW, Bayman L, Valestin J, Redd M, Lee YJ, Soubra M, et al. Lack of seasonal variation in the incidence of eosinophilic oesophagitis in adolescent and adult non-PPI-responsive oesophageal eosinophilia midwestern US populations. *United European Gastroenterol J*. 2014;2(2):69–76.
32. Sorser SA, Barawi M, Hagglund K, Almojaned M, Lyons H. Eosinophilic esophagitis in children and adolescents: epidemiology, clinical presentation and seasonal variation. *J Gastroenterol*. 2013;48(1):81–5.
33. Schlegel CR, Quintanilla NM, Olive AP, Minard CG, Davis CM. Relationship of pediatric eosinophilic esophagitis diagnosis to pollen and mold counts. *Ann Allergy Asthma Immunol*. 2014;113(3):321–2.
34. Elitsur Y, Aswani R, Lund V, Dementieva Y. Seasonal distribution and eosinophilic esophagitis: the experience in children living in rural communities. *J Clin Gastroenterol*. 2013;47(3):287–8.
35. Kagalwalla AF, Wechsler JB, Amsden K, Schwartz S, Makhija M, Olive A, et al. Efficacy of a 4-food elimination diet for children with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2017;15(11):1698–707.e7.
36. Lucendo AJ, Arias A, Redondo-Gonzalez O, Gonzalez-Cervera J. Seasonal distribution of initial diagnosis and clinical recrudescence of eosinophilic esophagitis: a systematic review and meta-analysis. *Allergy*. 2015;70(12):1640–50. **Systematic review which evaluated 18 studies involving 16,846 patients and found no relationship between seasonal variation and clinical symptoms, specifically food bolus impaction, and diagnosis of EoE.**
37. Lucendo AJ, Molina-Infante J, Arias A, Gonzalez-Cervera J. Seasonal variation in the diagnosis of eosinophilic esophagitis: there and back again. *J Pediatr Gastroenterol Nutr*. 2017;64(1):e25.
38. Pesek RD, Rettiganti M, O'Brien E, Beckwith S, Daniel C, Luo C, et al. Effects of allergen sensitization on response to therapy in children with eosinophilic esophagitis. *Ann Allergy Asthma Immunol*. 2017;119(2):177–83.
39. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol*. 2014;113(6):624–9.
40. van Rhijn BD, van Ree R, Versteeg SA, Vlieg-Boerstra BJ, Sprickelman AB, Terreehorst I, et al. Birch pollen sensitization with cross-reactivity to food allergens predominates in adults with eosinophilic esophagitis. *Allergy*. 2013;68(11):1475–81.
41. Simon D, Straumann A, Dahinden C, Simon HU. Frequent sensitization to *Candida albicans* and profilins in adult eosinophilic esophagitis. *Allergy*. 2013;68(7):945–8.

42. Hunter H, Wong T, Winstanley A, Till SJ. Eosinophilic esophagitis linked to pollen food syndrome. *J Allergy Clin Immunol Pract*. 2018;6(2):667–8.
43. De Swert L, Veereman G, Bublin M, Breiteneder H, Dilissen E, Bosmans E, et al. Eosinophilic gastrointestinal disease suggestive of pathogenesis-related class 10 (PR-10) protein allergy resolved after immunotherapy. *J Allergy Clin Immunol*. 2013;131(2):600–2.e1-3.
44. Wells R, Furman M, Fox A. Recurrence of eosinophilic oesophagitis with subcutaneous grass pollen immunotherapy. *Ann Clin Case Rep*. 2017;2:1227.
45. Atkins D, Furuta GT, Liacouras CA, Spergel JM. Eosinophilic esophagitis phenotypes: ready for prime time? *Pediatr Allergy Immunol*. 2017;28(4):312–9.