



Does Aeroallergen Sensitization Cause or Contribute to Eosinophilic Esophagitis?

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Abstract

Eosinophilic esophagitis is an atopic disease defined clinically by esophageal symptoms in combination with a dense esophageal eosinophilia. EoE is triggered and maintained by exposure to certain foods and it is known that dietary modification controls symptoms and achieves disease remission. Recently, aeroallergens have been implicated in the pathogenesis of EoE. To examine the role of aeroallergens in EoE, we reviewed the published literature. Sensitization and production of IgE antibodies to foods and aeroallergens in subjects with EoE has been demonstrated. However, the evidence suggests only a minor role for IgE-mediated immune reactions in EoE. There is some evidence to support an association of EoE diagnosis and flares with environmental allergen exposure, and animal studies support the notion that EoE may be induced by exposure to inhalant allergens. Some studies show that newly diagnosed cases of EoE follow a seasonal pollen distribution (summer and spring), but the weight of evidence does not support the seasonal occurrence of diagnosis or worsening of symptoms. Overall, we conclude that the current evidence does not support causality in inhalant allergen exposure and the genesis nor exacerbations of EoE in humans, although there is a possibility that inhalant allergen sensitization could play a modifying role in EoE in the context of cross-reacting food allergens.

Keywords Eosinophilic esophagitis · Aeroallergen · Pollen · Cross-reactivity

While the role of food allergy in the development of EoE is clear, there have also been a number of investigations and reports to interrogate the role of aeroallergen sensitization in EoE. EoE can be considered within the atopic disease diatheses, with inflammatory pathways involving release of IL-33, TSLP, and IL-5, and with activation and infiltration of T cells and eosinophils. Little evidence supports a role for IgE in the pathogenesis of EoE. Concomitant sensitization and production of IgE antibodies to foods and aeroallergens in subjects with EoE has been demonstrated [1–3], but it does not appear that IgE is critically involved in EoE pathology. The failure of omalizumab [4] and success of mepolizumab [5] starkly elucidates the lack of a critical role of IgE and to the importance

of eosinophils in EoE. Thus, can sensitization to inhalant allergens contribute to the pathology of EoE? The presence of IgE antibodies to inhalant and food allergens is common in allergic rhinitis, asthma, and type I food allergy syndromes such as urticaria, angioedema, anaphylaxis, and oral allergy syndrome (OAS). In EoE, skin prick testing (SPT) and serum IgE testing often do not identify the offending food allergens involved [6–8]. However, due to co-morbidity with other IgE-mediated atopic diseases, concomitant type I sensitization to inhalant and food allergens is not surprising. Upper airway exposure to inhalant allergens with subsequent esophageal contact via swallowing of secretions is a plausible route of exposure to the esophageal mucosa with subsequent sensitization or exacerbation of EoE.

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What Is the Evidence That Inhalant Allergens Play a Role on the Induction and Exacerbation of EoE?

Mishra et al. reported that intranasal aspiration of aspergillus antigen in mice, but not with oral or intragastric administration resulted in concomitant esophageal and pulmonary

eosinophilic inflammation [9]. Additional work by this group also demonstrated that an EoE-like inflammation is induced in murine models exposed to inhaled and intranasal allergens from dust mite and cockroach, but not cat and dog [10].

There have been some case reports and arguments put forth to suggest that inhalant allergen exposure and sensitization may be central to the causality and exacerbations of EoE. In a case report by Fogg et al., a 21-year-old patient with EoE was described, in which the esophageal disease appeared to flare during the pollen season (spring and summer) and remit in the pollen “off-season” (winter) [11]. Food allergen SPT and atopy patch testing (APT) were negative, but inhalant allergen testing was positive (trees, grasses, ragweed, aspergillus, cat, dog, and dust mite). Thus, it was proposed that the inhalant allergens were the putative EoE inciting agent(s) as they were thought to correspond to the seasonal flares of EoE in that patient.

Others have also reported seasonal variations in the diagnosis and flares of EoE as patient symptoms appeared to occur during specific pollen seasons [12, 13], but this has not been corroborated by all reports [14] (Table 1). A meta-analysis of these studies did not support a clear seasonal association with EoE flares, complications nor diagnosis [28]. Taking into account the difficulties in identifying and tracking esophageal eosinophilia, the overlap between inhalant allergen seasons versus perennial allergens, and pinpointing a specific culprit aeroallergen that induces the EoE flares, it may be difficult to draw clear conclusions from any of these reports.

Some authors have suggested that inhalant allergen sensitization plays a more prominent role in adults than in younger children with EoE [29]. This has been based, in part, on the fact that older children and adults demonstrate more IgE-associated aeroallergen sensitization [30, 31] and report that overall symptoms were worse in patients with concomitant aeroallergen sensitization [32]. The evidence that food elimination was an effective treatment was initially identified in children and initially thought not to be as effective in adults. However, subsequently, food elimination of essentially the same foods has been shown to be an equally effective strategy in adults [7, 33]. Mahdavinia et al. reported a higher incidence of pollen-associated food allergy syndrome (PFAS) in adults with EoE than subjects with other atopic conditions [34] and the incidence of EoE in children with IgE-mediated food allergy (urticaria, anaphylaxis, etc.) has been estimated at about 4.7% [35]. Thus, there appears to be an increased rate of IgE-mediated food allergy disorders in adults and children with EoE.

Some authors have posited that aeroallergen cross-reactivity occurs between pollen and food allergens, and the initial sensitization occurs via pollens with subsequent esophageal sensitization and inflammation [3]. Most of the evidence is borrowed from studies of IgE-mediated conditions such as

anaphylaxis and oral allergy syndrome; the evidence for EoE resulting from pollen sensitization is largely circumstantial. Van Rhin et al. suggested that pan-allergens, such as the PR-10 group (Bet v1), could lead to food reactions and EoE [36]. Subsequent work by this group used component-resolved diagnosis (CRD) to identify specific allergenic proteins as a guide to direct dietary elimination, but these trials failed to significantly improve EoE histology [37]. A small study of EoE subjects with positive IgE testing for grasses were studied to determine the effect of dietary elimination of wheat and rye to investigate the possibility that grass pollen sensitization may induce responses to cross-reacting allergens in wheat and rye, but the diet failed to show improvement in EoE symptoms [29].

Cases have been reported in which EoE occurred after the use of SLIT for hazelnut, birch, and alder [38] and oral immunotherapy for food allergy [1]. OIT-induced EoE carries an incidence rate of approximately 3% [6]. Pesek reported that children 6–11 years, who underwent therapy for EoE (oral corticosteroids and/or food elimination), had an increased remission failure rate if they were sensitized to perennial aeroallergens (primarily mold and cockroach) as identified by SPT [39]. This suggested that potential exposure to inhaled/swallowed allergens may contribute to EoE treatment failures.

What Is the Role of Aeroallergen Testing to Identify Potential Triggering Agents in EoE?

In part, the absence of accurate allergy testing to identify food allergens in EoE and the wide availability of IgE testing, which is not predictive of food allergen-induced EoE, has added to the confusion. Many authors have attempted to use IgE testing to suggest that cross-reacting pollen allergens may contribute to or cause EoE. Few have employed rigorous elimination trials of pollen cross-reacting food allergens. The ability of IgE testing (SPT, immunoCAP, CRD, etc.) to identify offending food allergens in EoE has been disappointing, while blind elimination and elemental diets consistently point to major food allergens as the primary inciting agents. APT has also been used to identify potential food allergens in EoE with mixed results. Spergel et al. reported encouraging results using SPT and APT to identify food allergens as confirmed by elimination and re-challenge of offending foods [40, 41]. They reported a sensitivity and specificity ranging from 50 to 95% for various food allergens [41]. Osterballe et al. reported that the sensitivity and specificity of APT was poor in identifying children with cow's milk protein allergy with or without eczema [42] and Philpott et al. concluded that SPT, IgE, total IgG, and APT failed to accurately identify food allergens as identified by an elimination diet [8]. Overall,

Table 1 Association between season and eosinophilic esophagitis

Author	Location	Period	Design	Age (years)	N	Outcome variable	Results
Fogg et al. [11]	Philadelphia, PA	1998–2000	Case review, longitudinal	21	1	Season of EoE diagnosis	Increased symptoms and worse histology during pollen seasons (spring and summer), resolution during winter
Wang et al. [15]	Indianapolis, IN	1998–2004	Retrospective, cross-sectional	0.2 to 19.5	234	Season of EoE symptoms and diagnosis	Increased symptoms and diagnoses in spring, summer, and fall as compared to winter
Prasad et al. [16]	Rochester, MN	1976–2005	Retrospective, cross-sectional	4–48	78	Season of diagnosis of EoE	Diagnosis of EoE was greatest in late summer and fall
Almansa et al. [17]	Jacksonville, FL	2007–2008	Retrospective, cross-sectional	> 19	41	Season of diagnosis of EoE	Increased number of diagnoses in summer and spring as compared to fall and winter
Moawad et al. [18]	Washington, DC	2006–2008	Retrospective, cross-sectional	> 19	127	Season of diagnosis of EoE	Most cases of EoE were diagnosed in the spring months
Wolf et al. [19]	Chapel Hill, NC	2012	Case series	20–40	3	Season of EoE onset and diagnosis after allergen exposures	Increased number of diagnoses of EoE after allergen exposure during spring months
Jensen [20]	USA (43 States, and Puerto Rico)	2009–2012	Retrospective, cross-sectional	> 21	524	Environmental or infectious etiologic factors for EoE	EoE is associated with seasonality, climate zone, and geographic factors. Increased number of diagnoses during summer and spring
Iwanczak [21]	Poland	2004–2009	Retrospective, cross-sectional	0.3–18	84	Seasonal distribution of EoE	Diagnosis of EoE was highest in spring and the lowest in winter
Elias et al. [22]	Rochester, MN	2000–2008	Retrospective, cross-sectional	> 17	372	Season of diagnosis of EoE	Peak diagnosis in December–January, less in May–June
Elitsur et al. [23]	West Virginia, Kentucky, and Ohio	2013–2010	Retrospective, cross-sectional	0–21	95	Seasonal trend of EoE diagnosis in rural communities	Diagnosis of EoE was evenly spread throughout the year without any seasonal preference
Chadha et al. [24]	Nashville, TN	2009–2012	Retrospective, cross-sectional	0–20	211	Season of diagnosis of EoE (endoscopy)	No seasonality association of EoE diagnosis
Sorser [25]	Detroit, MI	2001–2006	Retrospective, cross-sectional	0–21	44	Clinical presentation and seasonal variation of EoE	Tendency of EoE to be diagnosed in the fall, but there was no difference in seasonal onset of symptoms
Van Rhijn [26]	Netherlands	1996–2010	Retrospective, cross-sectional	> 21	674	Birch pollen sensitization with cross-reactivity to food allergens in EoE	No seasonal variation in diagnosis of EoE
Frederickson [27]	Iowa	2003–2013	Retrospective, cross-sectional	> 21	193	Comparison of EoE in an urban vs. rural environment	No seasonality association of EoE diagnosis

No highlight shows seasonal association of EoE. Yellow highlight shows no significant difference between seasons

APT and SPT testing-directed food elimination diet has resulted in a 45% success rate in identifying offending foods [33].

Clayton et al. have suggested a role for esophageal mucosal IgG4 as a potential mechanistic etiology in EoE after demonstrating elevated IgG4 tissue levels and specific IgG4 deposits in the esophageal mucosa [4]. As alternative pathways of immunologic activation towards food allergens must be operative, the presence of elevated levels of IgG4 directed against food allergens is interesting, although the well-described role of IgG4 in tolerance

induction could suggest a protective rather than a pathogenic role.

At this time, the current evidence that aeroallergen sensitization is substantially involved with causing and exacerbating EoE is weak. While it is intriguing to consider the possibility that cross-reacting allergens, such as pathogenesis related (PR) proteins, could play a contributing role in concomitant EoE with other atopic diseases such OAS or allergic rhinitis, it is likely that only a small subset of subjects are affected. The clear evidence that food elimination is an effective therapy for

EoE suggests that perhaps the major inciting allergens are derived from foods and secondarily from aeroallergen cross-reactivity. This said, attention must be paid to the potential worsening of EoE with exposure to cross-reacting inhalant allergens in the context of SLIT and when evaluating the effect of elimination diets on EoE outcomes.

Compliance with Ethical Standards

Conflict of Interest JRG and MAZ-B declare that they have no conflict of interest. EGB has received a research contract from ALK-Abello investigating allergen T cell epitopes and serves on the Scientific Advisory Board for United Allergy Services.

Research Involving Human Participants and/or Animals There is no research involving humans or animals

Informed Consent No human research.

Abbreviations EoE, eosinophilic esophagitis; SPT, skin prick test; SLIT, sub-lingual immunotherapy; OAS, oral allergy syndrome; APT, atopy patch test; PR, pathogenesis related; CRD, component-resolved diagnosis

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