



## Recurrence of Eosinophilic Oesophagitis with Subcutaneous Grass Pollen Immunotherapy

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### Abstract

Case reports have described an association between both oral food immunotherapy and aeroallergen immunotherapy with the development of Eosinophilic Oesophagitis (EoE). The underlying mechanism of this is poorly understood, as is the possible role that both food and aeroallergen sensitization play in the pathogenesis of EoE.

Specific Immunotherapy has a longstanding history of use in the management of moderate to severe seasonal allergic rhinitis, caused by tree or grass pollens. Subcutaneous immunotherapy (SCIT) to grass pollen is less commonly used in children than sublingual (SLIT) or oral immunotherapy for practical reasons.

Here we describe a case of a child with severe grass pollen related allergic rhinitis as well as known but quiescent EoE, who developed recurrence of oesophageal symptoms on two separate occasions coincident with the commencement of sublingual immunotherapy (SLIT) to grass pollen. He was subsequently started on subcutaneous immunotherapy (SCIT) to grass pollen and again developed recurrence of symptoms of EoE – a phenomenon that has yet to be reported in the medical literature.

### Background

A rise in the prevalence and recognition of EoE has been seen alongside the rise in IgE mediated allergic disease in western countries, and concomitant allergic diseases such as asthma, allergic rhinitis and eczema are common in children with EoE [1]. The role of IgE food sensitization in patients with EoE is unclear but elemental diets are often used in its management with strong evidence of success [2].

Aeroallergens have also been linked to the development of EoE. Mishra et al. [3] described an aetiological role for aeroallergen exposure in animal models. Other studies have observed a correlation between season and symptoms of EoE, supporting the link between aeroallergens and the development of EoE [4-6].

Specific Immunotherapy has a longstanding history of effective use in the management of moderate to severe seasonal allergic rhinitis, caused by tree or grass pollens when maximal pharmacotherapy with intranasal steroids and anti-histamines has provided inadequate symptom relief. In the UK, subcutaneous immunotherapy (SCIT) to grass pollen is less commonly used in children than sublingual (SLIT) immunotherapy for practical reasons, but still offers an alternative treatment option for children whom may not tolerate SLIT or for those in whom it is not tolerated, adhered to or contraindicated.

An association between initiation of oral food immunotherapy and the development of EoE has been reported. A systematic review by Lucendo et al. [7] found that new onset EoE developed in up to 2.7% of patients undergoing oral immunotherapy for food allergy. Case reports have also described the association between pollen sublingual immunotherapy and the development of EoE [8]. However, the authors could not find any case reports in the literature describing the development or recurrence of EoE following SCIT for anaero allergen.

### Case Presentation

A 10-year-old boy was reviewed in our allergy clinic for consideration of immunotherapy to grass pollen. He had a history of nut allergy, allergic rhinitis, atopic asthma and eosinophilic oesophagitis.

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Asthma was reported to be seasonal and was well controlled on inhaled steroid (fluticasone 200 mcg inhaled, twice daily), with normal spirometry.

Eosinophilic oesophagitis was diagnosed histologically at age 8 with 45 eosinophils per high power field in the lower oesophagus on endoscopy. Symptoms were reported to be seasonal and our patient was treated with viscous budesonide and omeprazole for flares. Skin prick testing showed sensitization to grass pollen (12 mm), house dust mite (7 mm) and alternaria (7 mm).

At the time of review (in the autumn), symptoms of EoE were under control.

Seasonal allergic rhinitis was sub-optimally managed with a nasal fluticasone furoate spray (27.5 mcg), montelukast 5 mg and an oral antihistamine. Our patient had previously been commenced on sublingual immunotherapy to grass pollen (5 grass mix, Staloral, Stallergenes) on two occasions, but had been unable to tolerate treatment due to recurrence of symptoms of EoE.

The first trial of SLIT, 10 months previously, had resulted in abdominal pain and symptoms of reflux two hours after the first dose. The dose was reduced and he was advised to spit out the extract after 2 minutes. Despite this, his abdominal pain and symptoms of reflux persisted. The clinical impression was that of recurrence of EoE and therefore the SLIT was stopped after one week. He was recommenced on budesonide slurry for three weeks with resolution of symptoms of EoE.

The second trial of SLIT immunotherapy was commenced two months later on a slower up-dosing regimen with preventative protection with viscous budesonide and omeprazole. Our patient tolerated up-dosing to maintenance dose over 3 months but he could not tolerate a decrease in the viscous budesonide on this dose.

The family were determined that the patient should receive desensitization treatment, and thus he received a trial of subcutaneous immunotherapy (SCIT) to grass pollen. The patient tolerated the first two injections of 0.1 and 0.2ml (Allergovit, grass pollen) but developed reflux symptoms following the third dose (0.4 ml). After the fourth injection (0.8 ml) he developed significant vomiting, warranting an inpatient stay in hospital and a course of oral steroids. Despite no further SCIT, symptoms of EoE worsened over the following month, requiring another inpatient hospital stay, further oral steroids and elemental diet. A repeat endoscopy was not performed since symptoms were consistent with his initial presentation of EoE and improved with steroid treatment.

At review the following month symptoms had settled and further immunotherapy has not been recommenced.

## Discussion

The role of aeroallergens in the pathogenesis of EoE has yet to be established. However, seasonal differences in disease prevalence and recurrence have been reported and case reports have described recurrence of symptoms of EoE associated with SLIT to aeroallergens.

We have described the first case in the literature of recurrence of EoE following SCIT. We suggest that the exposure to subcutaneous aeroallergen immunotherapy induced a similar immune response to SLIT, resulting in recurrence of EoE. The exact mechanism underlying this is not fully understood but, in this case, cannot be as a result of the direct exposure of the allergen on the oesophageal mucosa. Patients

with a history of EoE whom are offered immunotherapy (both SCIT and SLIT) should be counseled about the risk of recurrence of disease.

Further studies are needed to help understand the role of aeroallergens in the development of EoE and may help to identify individuals at higher risk.

The possibility of using immunotherapy as a treatment option for EoE in children has been described [9] but requires a better understanding of the disease, and further studies, before this could be a realistic option.

Eosinophilic esophagitis (EoE) is an emerging clinicopathologic entity defined by abnormal esophageal eosinophilic infiltration. Management of this disease is hampered by limited understanding of etiologic and controllable risk factors. The aim of this systematic review was to determine the environmental risk factors for EoE. We searched the PubMed, Web of Science, and EMBASE databases from January 1, 1950, through June 30, 2015. To identify additional relevant studies, we had searched bibliographies of included articles. We limited the review to articles using human subjects and consisting of case reports, case series, cross-sectional and cohort studies, and clinical trials. Nineteen articles discuss the risk of environmental exposures on EoE and indicate that environment plays a large role in the etiology of EoE. Seasonal, geographic, and climate-based differences in disease prevalence have been reported, but the exact mediators of this process, possibly aeroallergens that vary over time and from place to place, remain elusive.

## Background 1

Seasonal variation has been reported in diagnosis of eosinophilic oesophagitis (EoE), but results are not consistent across studies and there are no national-level data in the USA. AIM: To determine if there is seasonal variation in diagnosis of oesophageal eosinophilia and EoE in the USA, while accounting for factors such as climate zone and geographic variation.

## Methods

This was a cross-sectional study using a USA national pathology database. Patients with oesophageal eosinophilia ( $\geq 15$  eosinophils per high-power field) comprised the primary case definition and were compared to those with normal oesophageal biopsies. We calculated the crude and adjusted odds of oesophageal eosinophilia by season, as well as by day of the year. Sensitivity analyses were performed using more restrictive case definitions of EoE, and after stratification by climate zone.

## Results

Exactly, 14 524 cases with oesophageal eosinophilia and 90 459 normal controls were analyzed. The adjusted odds of oesophageal eosinophilia were higher in the late spring and summer months, with the highest odds in July (a OR: 1.13; 95% CI: 1.03-1.24). These findings persisted with increasing levels of oesophageal eosinophilia, as well as across EoE case definitions. Seasonal variation was strongest in temperate and cold climates, and peak diagnosis varied by climate zone.

## Conclusions

There is a mild but consistent seasonal variation in the diagnosis of oesophageal eosinophilia and EoE, with cases more frequently diagnosed during summer months. These findings take into account climate and geographic differences, suggesting that aeroallergens may contribute to disease development or flare.

## Background 2

The onset of eosinophilic esophagitis (EoE) after oral immunotherapy (OIT) has been repeatedly described in patients with immunoglobulin E (IgE)-mediated food allergy in recent years, but the relation between the 2 conditions has not been fully assessed and quantified.

### Objective

To provide a systematic review of the evidence for an association between OIT and EoE.

### Methods

Electronic searches were performed with keywords relating to EoE and OIT in the MEDLINE, EMBASE, and SCOPUS databases. Summary estimates were calculated. A fixed-effects model was used depending on heterogeneity ( $I(2)$ ). Risk of publication bias was assessed by funnel plot analysis and the Egger test.

### Results

The search yielded 118 documents, 15 of which were included in the quantitative summary. Most reported information came from children undergoing peanut, milk, and egg OIT. Significant publication bias in favor of studies reporting the development of EoE after OIT was documented. The overall prevalence of EoE after OIT was 2.7% (95% confidence interval 1.7%-4.0%,  $I(2) = 0\%$ ). Differences between medium-to high-quality studies and those of low quality were documented (3.5% vs. 2.5%, respectively). EoE often resolved after OIT discontinuation; histologic remission of EoE achieved after allergen immunotherapy also was documented in 2 patients whose topical fluticasone treatment failed.

### Conclusion

New onset of EoE after OIT occurs in up to 2.7% of patients with IgE-mediated food allergy undergoing this treatment strategy. The limited data on the utility of allergen immunotherapy as a therapy for EoE prevent a recommendation for this treatment option.

Eosinophilic esophagitis (EoE) may affect humans at any age with a predominance for Caucasian males. The clinical manifestation of EoE varies depending on the patient's age. Infants and young children may primarily present with unspecific symptoms such as feeding problems, vomiting and abdominal pain. In adolescents and adults, dysphagia and food impaction become the predominant symptoms. EoE should also be considered in cases of refractory heartburn in both children and adults. Concomitant allergic diseases such as asthma, rhinitis and eczema, as well as peripheral eosinophilia and elevated total serum IgE values are common in pediatric and adult EoE patients. EoE seems to be primarily a food antigen-driven disease, whereas in adults, aeroallergen sensitization may dominate. Endoscopic features of EoE include mucosal edema, furrows, exudates, corrugated rings, strictures, and the so-called crepe paper sign. There appears to be a shift from an inflammatory-predominant phenotype in young childhood towards a more fibrotic phenotype in adolescents and adults. Long-term follow studies suggest that EoE is a chronic and potentially progressive disease causing recurring dysphagia in the majority of cases. The prevalence of strictures significantly increases with the duration of untreated disease, stressing the importance of early diagnosis and consequent treatment of EoE.

Sublingual immunotherapy (SLIT) is increasingly investigated and utilized for the treatment of food and pollen allergies. Previous case reports suggested that eosinophilic esophagitis (EoE) might

develop as a long-term complication in children after completion of oral immunotherapy. Here, we describe a 44-year-old female with a medical history of pollinosis who for the first time in her life developed complete manifestation of EoE (peak eosinophils 164/high power field) 4 weeks after initiation of SLIT using specific soluble allergens (hazelnut, birch, alder) according to previous specific serum IgE testing. After discontinuation of SLIT, EoE resolved completely within 4 weeks without any other medical intervention. During a follow-up of 12 months the patient remained free of any esophageal symptoms. This is the first case report demonstrating a close and therefore likely causative association between pollen SLIT and EoE in an adult patient.

Eosinophil infiltration into the esophagus is observed in diverse diseases including gastroesophageal reflux and allergic gastroenteritis, but the processes involved are largely unknown. We now report an original model of experimental esophagitis induced by exposure of mice to respiratory allergen. Allergen-challenged mice develop marked levels of esophageal eosinophils, free eosinophil granules, and epithelial cell hyperplasia, features that mimic the human disorders. Interestingly, exposure of mice to oral or intra gastric allergen does not promote eosinophilic esophagitis, indicating that hypersensitivity in the esophagus occurs with simultaneous development of pulmonary inflammation. Furthermore, in the absence of eotaxin, eosinophil recruitment is attenuated, whereas in the absence of IL-5, eosinophil accumulation and epithelial hyperplasia are ablated. These results establish a pathophysiological connection between allergic hypersensitivity responses in the lung and esophagus and demonstrate an etiologic role for inhaled allergens and eosinophils in gastrointestinal inflammation.

## Background 3

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.

## Purpose of Review

Eosinophilic esophagitis is a recently recognized disorder receiving increasing attention. Patients present with symptoms of gastroesophageal reflux and are not responsive to standard or aggressive reflux medications. This article reviews all literature published in English from December 2005 to November 2006 from PubMed on the topic of eosinophilic esophagitis.

## Recent Findings

Three articles have confirmed that food allergies are causative in more than 90% of patients. Three different diet strategies were used: elemental, elimination diet based on the prick-skin test, and the atopy patch test or removal of the six most common foods. The elemental diet had the highest success rate (> 95%), whereas the testing-based elimination diet (> 75%) and six-food elimination diet (> 70%) had lower success rates. There are no organized dietary trials in adults.

## Summary

Recent literature on pediatric patients with eosinophilic esophagitis confirms that nearly all patients respond to an elemental diet with resolution of symptoms and normalization of biopsies. Although diets based on testing or removal of the most common allergens showed success, they were less successful than a complete elimination diet. Unfortunately, there are very limited studies in adults that address this issue.

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