

Eosinophilic Esophagitis due to Aeroallergens: A Systematic Review and Update

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■ Abstract

Eosinophilic esophagitis is a chronic antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by T_H2 inflammation (at least 15 eosinophils/high power field) when other secondary systemic and local causes of esophageal eosinophilia are excluded. Although this disease was initially ascribed to a delayed reaction to food allergens, emerging evidence suggests that aeroallergens may also play a role in pathogenesis and disease course.

Some studies support seasonal variations in the diagnosis of eosinophilic esophagitis and disease exacerbations owing to the increase in aeroallergens to which patients are sensitized. It is also known that this disease can be caused by extensive, identifiable exposure to aeroallergens and after treatment with specific immunotherapy based on food or aeroallergens. It was recently postulated that treatment of allergic rhinoconjunctivitis can improve the symptoms of eosinophilic esophagitis, although data are limited to case reports and small series. Currently, biomarkers and biologic therapies are not helpful for diagnosis or inducing clinical and histological remission of the disease. Nevertheless, there are high hopes for dupilumab.

This review aims to give visibility to the involvement of aeroallergens in the triggering and exacerbation of eosinophilic esophagitis, since many of them, in addition to being airborne and inhalant, can also be ingested as food. Clearly, we must try to identify the cause of the disease to ensure remission.

Key words: Eosinophilic esophagitis. Aeroallergens. Rhinitis. Pollen. Asthma.

■ Resumen

La esofagitis eosinofílica es una enfermedad esofágica crónica mediada por antígenos, caracterizada por síntomas relacionados con disfunción esofágica e histológicamente por inflamación $Th2$ (al menos 15 eosinófilos/campo de gran aumento), cuando se excluyen otras causas secundarias sistémicas y locales de eosinofilia esofágica. Aunque esta enfermedad se atribuyó inicialmente a una reacción tardía a alérgenos alimentarios, la evidencia emergente sugiere que los aeroalérgenos también pueden desempeñar un papel en su patogénesis y evolución.

Hay estudios que avalan la variación estacional en el diagnóstico de esofagitis eosinofílica y exacerbaciones de la enfermedad en relación con el aumento de aeroalérgenos a los que los pacientes están sensibilizados. También se sabe que esta enfermedad puede generarse tras una gran exposición identificable de aeroalérgenos y tras un tratamiento con inmunoterapia específica con alimentos o aeroalérgenos. Recientemente, se ha postulado que el tratamiento de la rinoconjuntivitis alérgica puede mejorar los síntomas de la esofagitis eosinofílica, aunque los datos se limitan a informes de casos y series pequeñas. Actualmente, los biomarcadores y los tratamientos biológicos no son útiles para el diagnóstico, ni para inducir la remisión clínica e histológica de la enfermedad, aunque hay grandes esperanzas para dupilumab. El objetivo de esta revisión es dar visibilidad a la implicación de los aeroalérgenos en el desencadenamiento y/o exacerbación de la esofagitis eosinofílica ya que muchos de ellos, además de estar en el aire y poder inhalarlos, también podemos ingerirlos como parte de la comida. Es importante resaltar que, siempre que podamos, debemos tratar de descubrir la causa de la enfermedad, ya que es crucial para la remisión de la misma.

Palabras clave: Esofagitis eosinofílica. Aeroalérgenos. Rinitis. Polen. Asma.

Methods

We performed a literature search using Medline, PubMed, CINAHL, Embase, and Scopus. The search ran from 1993, when eosinophilic esophagitis was first described by a general practitioner, to 12-31-2021.

The keywords were *aeroallergens (environmental, occupational, and allergens)*, combined with *esophageal eosinophilia and eosinophilic esophagitis (children and adults), epidemiology, etiopathogenesis, environment, specific immunotherapy, genetics, immunology, pathophysiology, atopy, allergy (IgE and nonIgE mediated), typical and atypical symptoms, complications, comorbidities, natural history, diagnosis (clinical, endoscopic, histological, and differential), food allergens, atopic comorbidities (asthma, rhinitis, atopic dermatitis, and food allergy), gastroesophageal reflux disease, and therapy/treatment/management (esophageal dilation, food elimination diets, proton pump inhibitors drugs, corticosteroids, and avoidance measures)*. More than 125 articles were reviewed; of these, almost 60% were published during the last 5 years of the search period.

Manuscripts were selected by order of preference as follows: randomized controlled trials, systematic reviews, reviews, cohort studies, case-control studies, observational studies, cross-sectional studies, case reports, and single case reports. Prospective studies were also preferred over retrospective studies. We found high agreement between publications on the same features and outcomes in eosinophilic esophagitis due to aeroallergens and selected the most recent and best-designed studies.

1. Definition and Introduction

Eosinophilic esophagitis (EoE) is a clinical-pathological entity defined as a chronic esophageal disease caused by antigen-mediated food allergens (FA-EoE) and aeroallergens (AA-EoE). The latter, albeit to a much lesser extent, is characterized clinically by symptoms related to esophageal dysfunction and histologically by an eosinophil-predominant T_H2 inflammation. Other secondary systemic and local causes of esophageal eosinophilia are excluded [1,2].

Allergic reactions to foods affecting the gastrointestinal tract were reported by Hippocrates, who observed that cow's milk could cause urticaria, diarrhea, vomiting, and failure to thrive in infants and resolved when cow's milk was removed from their diet [3,4]. Nowadays, gastrointestinal immune reactions to cow's milk proteins that are mediated by T lymphocytes with or without the contribution of specific IgE antibodies are estimated to account for up to 40% of cow's milk protein allergies in infants and young children [3,5].

As with food protein-induced enterocolitis syndrome, EoE is a type of non-IgE-mediated food allergy affecting the gastrointestinal tract. Current evidence indicates that cell-mediated responses are essential in both diseases, whereas the role of IgE antibodies to the triggering allergens is minimal [3,6]. Diagnosis of EoE relies on clinical and histologic findings and exclusion of causes that show increased eosinophils in the gastrointestinal tract and systemic

involvement, as in parasitic intestinal infections, inflammatory bowel disease, celiac disease, achalasia, hypereosinophilic syndrome [7], and eosinophilic granulomatosis with polyangiitis [8].

2. Historical Perspectives

During the 1980s, some authors interpreted the presence of eosinophils in the esophageal mucosa as a histological marker of gastroesophageal reflux disease (GERD) [9]. Attwood et al [10] in the USA (1993) and 1 year later Straumann et al [11] in Switzerland defined EoE as an entity with its own clinical and histological characteristics. Kelly et al [12] described 23 children with GERD refractory to medical treatment and fundoplication who responded to treatment with an elemental diet. The first consensus guidelines on EoE were published in 2007 [13] and updated in 2011 [14]. Between both consensus, the presence of GERD had to be ruled out to confirm the diagnosis of EoE. In 2011, it was no longer necessary, since EoE and GERD were not mutually exclusive, with both entities able to coexist in the same individual. In addition, the existence of EoE responsive to proton pump inhibitors (PPIs) was recognized [13,14].

The American College of Gastroenterology (2013) and the European and American Societies of Pediatric Gastroenterology (2014) [15] published their guidelines for the management of EoE. The European guidelines on EoE also provided evidence-based statements and recommendations for diagnosing and treating children and adults [16]. In 2018, the Updated International Consensus Diagnostic Criteria Proceedings of the AGREE Conference were published [17]. EoE was initially recognized as a form of food allergy. In 2001, studies based on murine models showed that it could also be triggered by aeroallergens [18].

3. Epidemiology

The epidemiology of EoE is increasingly reported, along with cumulative research assessing environmental exposures associated with the disease and susceptibility due to genetic variants [19]. The incidence of EoE is approximately 1/10 000 new cases per year, and the increase in incidence is outpacing increases in identification and endoscopy volume. Still, the reasons for this increased interest in epidemiology are not yet fully delineated [20]. The incidence of EoE is 5-10 new cases per 100 000 inhabitants per year, and the disease now affects more than 1 out of 1000 people [19]. Other authors reported similar incidence rates, although prevalence has been reported to be between 10 and 57 cases/per 100 000 persons [21]. No data have been published on the epidemiology of AA-EoE.

Our personal experience is that, from a registry of 386 patients diagnosed with EoE (2012-2021), AA-EoE was confirmed in 5 cases, 3 of which were caused by occupational aeroallergens (oAA-EoE) [22-24] (Table 1). The remaining 2 have not been published. One involves oAA-EoE (Table 1), and the other involves sublingual immunotherapy initiated for EoE caused by pollens. All patients with oAA-EoE

also experienced occupational allergic respiratory disease, specifically, allergic rhinoconjunctivitis (ARC) and bronchial asthma.

Therefore, the general frequency of AA-EoE in our series is around 1.3% (5/386), and the frequency of oAA-EoE is about 1% (4/386).

Table 1. Description of Patients with Eosinophilic Esophagitis due to Perennial Occupational Aeroallergens

Patients	JACI	JIACI	Arch Broncon	Not published
Age, y	31	39	49	53
Sex	Female	Female	Male	Female
Occupation	Baker	Nursery school cook	Baker	Churros factory
o-AA to which patient is exposed and responsible for symptoms	WF (gliadin)	Proteins from yolk, chicken meat, and feathers (α -livetin)	Gluten	WF
The latency period between first exposure to o-AA and onset of symptoms:				
- Respiratory	23	1	30 y	2 y
- Digestive	26	7	Simultaneously	3 y
Allergy comorbidities	o-RC&BA to allergy WF	- Egg-bird syndrome - o-RC&BA to α -livetin protein	o-RC&BA to allergy WF	o-RC&BA to allergy WF
Sensitizations to other allergens:				
-Aeroallergens	Pollens	α -livetin	None	None
-Aeroallergens	None	Doubtful to mites	None	Anisakis
Digestive symptoms	Dysphagia, choking, and food impaction	Dysphagia, choking, and food impaction	Dysphagia, choking, and food impaction	Dysphagia
Gastroesophageal reflux disease	No	No	No	Initially classed as GERD but never confirmed
Response to treatment with omeprazole	No	No	Yes	20 mg/d: No response 40 mg/d: Response over 2 y Later, 80 mg/d: No response
Remission of EoE	Yes, after no exposure to heat flow at work	Yes, at first, without eating chicken (not working). 3 months later, no remission (at work)	-	Yes, after no exposure to heat flow at work
No exposure to triggering inhaled aeroallergens	Remission of EoE	No remission of EoE	No remission of EoE	Remission of EoE
No exposure to and no intake of triggering aeroallergens	Remission of EoE	Remission of EoE	Remission of EoE	Remission of EoE
Course	Asymptomatic, no respiratory or digestive symptoms, no exposure to WF	Asymptomatic on vacation and on sick leave, without eating chicken	Asymptomatic, no respiratory or digestive symptoms without exposure to WF, and without eating chicken	Asymptomatic on sick leave and reappearance of symptoms a month after starting work
Esophagoscopy with biopsy after removal of the triggering aeroallergen	Remission of EoE	In remission, if no exposure to or ingestion of causal allergen	Remission of EoE	Remission of EoE 1 mo after cessation of exposure to WF and recurrence of symptoms on re-exposure to WF
Current work situation	None (retired) by occupational disease	Continues working because she is self-employed	None (retired) owing to occupational disease	Not retired owing to problems not related to her occupation
Current treatment	None	STC (400 μ g/12 h) with partial response	None	As she is exposed, treatment with STC (400 μ g/12 h) and total response

Abbreviations: EoE, eosinophilic esophagitis; o-AA, occupational aeroallergen; o-RC&BA, occupational rhinoconjunctivitis and bronchial asthma; PR, partial response; STC, swallowed topical corticosteroids; TR, total response; WF, wheat flour.

4. Etiology and Pathogenesis

The etiology and pathogenesis of EoE are multifactorial, involving mainly environmental causes. It can be triggered by food and, to a lesser extent, by aeroallergens. Both can induce a delayed T_H2 hypersensitivity response [25].

4.1 Environmental Factors

Available evidence on the potential role of environmental factors' in EoE is limited. Studies were conducted in circumscribed regions or countries, such as the USA or Spain, where EoE is common. These studies represent only a tiny portion of the world and not areas with low prevalence [25].

EoE appears to be frequent in families, although studies in twins give more importance to the role of concurrent environmental exposure than to genetic heritability [25,26]. Environmental factors, such as maternal fever during pregnancy, cesarean delivery, and preterm delivery were associated with future development of the disease [25,27]. In addition, consumption of antibiotics in infancy might increase the risk of EoE in adulthood [25,28]. EoE may be considered a late manifestation of the atopic march [19,25,29], since patients with EoE frequently have atopic comorbidities. In one study, 74% of patients were sensitized to allergens. In comparison, 91% were sensitized to pollens, and reported concomitant allergic diseases included ARC, asthma (74%), IgE-mediated

food allergy (IgE-FA) (49%), and atopic dermatitis (AD) (7%) [30].

The mechanisms of immune activation in EoE continue to be investigated because they remain poorly known and triggering antigens can be challenging to identify [31]. Aeroallergens can be the sole driver of esophageal eosinophilia (EE) in some patients and can exacerbate existing EoE in others [32,33].

Despite disease manifestations being initially attributed to a delayed reaction to a food allergen, emerging evidence suggests that modifiable host factors and exposure to aeroallergens may also play a critical role in the pathogenesis of EoE [34].

A series of findings have been reported with respect to aeroallergens [34].

4.1.1 EoE can appear during aeroallergen-based sublingual immunotherapy or aeroallergen-based subcutaneous immunotherapy

In the literature, case reports linked aeroallergen-based sublingual immunotherapy to new-onset EoE [34]. The first association between sublingual immunotherapy and EoE was reported in an adult with ARC treated with sublingual immunotherapy (hazelnut, birch, and alder). Symptoms of classic EoE developed within 4 weeks of initiation of therapy, and esophageal biopsy revealed 164 eosinophils per high power field. EoE remitted 4 weeks after discontinuation of sublingual immunotherapy. Follow-up at 1 year revealed

Table 2. Cases of Eosinophilic Esophagitis (EoE) Suspected of Being Triggered by Aeroallergens^a

	pAAs-EoE1	pAAs-EoE2	pAAs-EoE3	cAA-EoE
Sex	Female	Female	Male	Male (3 brothers)
Age, y	10	28	31	38, 35, 33
Symptoms	Choking, dysphagia, and fear of intake of food	Dysphagia and cough in spring	Dysphagia in spring	Dysphagia and choking
Eosinophils/high power field	15	100	45	34, 55, 22
Sensitization to aeroallergens	Pollen	Pollen	Pollen	Cat and dog epithelium
Suspected aeroallergen triggering EoE	Preseasonal sublingual immunotherapy (pollen)	Environmental pollen	Environmental pollen	Cat epithelium
Symptoms without exposure to aeroallergen (2 mo)	Asymptomatic	Dysphagia	Asymptomatic	Dysphagia and choking
No exposure to aeroallergens (2 months)	Remission of EoE	No remission of EoE	Remission of EoE	No remission of EoE
Re-exposure to aeroallergen	Not performed	Remission of EoE	Remission of EoE	No remission of EoE
Treatment with a food elimination diet	Not performed	No remission of EoE	Not performed	No remission of EoE
Three years later	Asymptomatic	Asymptomatic, following an elimination diet (cow's milk and legumes)	Asymptomatic EoE, spontaneous remission of EoE	EoE, remission with swallowed topical corticosteroids

Abbreviations: cAA-EoE, eosinophilic esophagitis triggered by cat epithelium; p-AAs-EoE1, eosinophilic esophagitis triggered by pollen; p-AAs-EoE2 and 3, eosinophilic esophagitis not triggered by pollen.

^aConfirmed in only 1 patient (EoE triggered by sublingual immunotherapy to pollen).

no signs of EoE [35]. EoE was subsequently reported after sublingual immunotherapy with grass tablets and dust mite, remitting after discontinuation [36,37]. In another case report, the authors reported EoE caused by grass pollen-based sublingual immunotherapy with tolerance to the same pollens with subcutaneous immunotherapy [38]. In addition to the previous 2 case reports, the literature review revealed, a further 5 case reports, 4 of which had EoE triggered by pollen sublingual immunotherapy (one of them also developed EoE with subcutaneous immunotherapy) and the other by latex. Another case series was recently published [36]. We provide data on a case of AA-EoE due to pollen (Table 2).

4.1.2 Seasonal variation in EoE diagnosis and flares

The lack of response to treatment with a food elimination diet (FED) in a percentage of EoE patients suggests that antigens other than food allergens may be involved [18,39,40]. There are studies both for and against the seasonality of diagnosis of EoE, most of them correlating with the pollen season. However, some did not report said seasonality in diagnosing this disease. We discuss most of them below [40].

The first study was in murine models of EoE induced by initial sensitization followed by intranasal challenges of sensitized mice with the corresponding aeroallergens, such as *Aspergillus fumigatus*, dust mite, and cockroach. The authors suggested that intranasal exposure to AAs leads to topical delivery of the antigens to the esophagus and subsequent development of EoE [18,39,40].

Fogg et al [32] demonstrated the correlation between EoE activity and seasonal aeroallergens in a case report with repeated endoscopies in an adult patient who experienced spontaneous disease remission and recurrence of disease correlating with the pollen season.

Another study shows a seasonal variation in the diagnosis of EoE, with more cases diagnosed during the spring months. These findings are related to the increase in aeroallergens and pollen distribution during the spring months in Oklahoma, USA [41].

Akei et al [42] report the first evidence that percutaneous exposure to allergens primes for EoE through a potent T_H2 -dependent mechanism.

One study observed esophageal eosinophilic infiltration in patients with respiratory allergy during the symptomatic period. Based on biopsy specimens, the authors found that 26% of patients with ARC without GERD had EoE during active allergy respiratory symptoms. Eosinophil counts are higher in patients with ARC during the pollen season than in healthy controls. However, the number was lower than observed in patients with EoE [39,40,43].

A study performed in New York, USA demonstrated a seasonal correlation between peak grass pollen levels and peak onset of EoE symptoms, both of which were highest from July to September. Of the 11 pollen taxa examined at each center, only grass pollen correlated with EoE [44].

Some researchers detected seasonal variation in winter, a low outdoor allergen season, with the lowest number of newly diagnosed EoE patients [45]. Other authors who evaluated esophageal bolus impaction found an increase in cases in summer and fall [46].

Moawad et al [47] noted a significant association between diagnosis and grass pollen prevalence. However, the authors did not report an association with a tree or weed pollen count [39].

Almansa et al [48] performed a retrospective review on adults with EoE for 1 year and found a significant increase in diagnoses in the spring and summer compared to the fall [39].

Prasad et al [49] noted an increased prevalence of EoE in the late summer/fall that paralleled the increase in endoscopy volume.

In a study of patients with EoE, 14% were suspected of having aeroallergen-associated triggers of EoE based on the clinical history; of these, 20% had a biopsy-confirmed variation of EE triggered by aeroallergens. All patients had ARC. Since children with EoE and allergic rhinitis might experience exacerbations of their EE during certain seasons depending on the specific aeroallergens to which they are sensitized, identifying aeroallergens in sensitized patients is essential and can guide therapy [33]. These findings demonstrate that there may be a subset of patients with EoE and ARC in whom aeroallergens can contribute to flares of EoE [39].

Sorser et al [50] reviewed all esophageal biopsies performed between 2001 and 2006 on patients aged under 21 years, of whom 5.8% had EoE; no seasonal correlation or correlation between the onset of symptoms and seasons was observed [50].

Schlegel et al [51] found no association between a diagnosis of EoE in pediatric patients and pollen and fungi counts. In addition, the percentage of EoE diagnoses was evenly distributed compared to the total number of biopsies, without seasonal variation. Another group of researchers demonstrated no seasonal preference in diagnosing EoE in children living in rural communities [52]. Similarly, Kagawalla et al [53] noted no seasonal influence in other pediatric populations.

Lucendo et al [54] performed a systematic review to determine the relationship between seasonal variations and clinical symptoms (food bolus impaction) and diagnosis of EoE. No statistically significant differences were noted between seasonal variation and either EoE diagnoses or food bolus impaction. Elsewhere, sensitization to perennial aeroallergens and fungi was thought to lead to nonresponse to EoE treatment in some patients. Therefore, additional studies are needed to further understand the effect of aeroallergens on EoE [55].

A single case series of adults demonstrated new-onset EoE following high exposure to aeroallergens, including dust mites, pollen, and fungi. However, allergic sensitization to the triggering antigen was only demonstrated in 1 patient. In addition, since these 3 patients have not been followed up, nothing is known about the evolution of AA-EoE [56].

Since 2012, our group has tried to reach the diagnosis of EoE triggered by aeroallergens (mites, fungi, epithelia, and pollens). We have had several suspected cases, although only 1 has been confirmed (Table 2). Nevertheless, we ask all the patients with EoE when they come in for a check-up if their symptoms of esophageal dysfunction (SED) worsen during the pollen season.

In our case reports, oAA-EoE and aeroallergens (wheat flour, α -livetins, and pollen) are triggers of EoE. In no cases do they exacerbate pre-existing EoE due to other causes.

We agree with various authors [34,39] that both triggering of AA-EoE and exposure to aeroallergens require patients to have allergic rhinitis for the allergens to be transported in nasal secretions and post-nasal drip to the esophagus.

4.1.3 EoE can occur after significant and identifiable exposure to aeroallergens

The 3 cases of oAA-EoE we report [22-24] (Table 1) were exposed to a high concentration of aeroallergens for at least 40 hours a week. We have no experience in patients with onset of symptoms consistent with EoE after a single exposure to high concentrations of aeroallergens.

We agree with the emerging hypothesis that treatment of allergic rhinitis may improve symptoms of EoE, although current data are limited to case reports and small series [34].

On the other hand, topical nasal corticosteroids used for the control of allergic rhinitis could be helpful in the management of EoE by reducing nasal secretions and postnasal drip, thus decreasing the number of aeroallergens retained in the nose and those that reach the esophagus. Few data support or oppose this possibility. Further studies are necessary to determine whether nasal sprays influence the induction of remission, disease control, and symptomatic relief in EoE [34].

We would also add from our experience that allergic rhinitis must be moderate-severe with significant nasal obstruction. Faced with this situation, patients are forced to breathe through their mouths, thus inhaling aeroallergens. In our study, patients with AA-EoE had such severe nasal obstruction that it was also accompanied by intermittent anosmia and a steady nasal voice [22-24].

Occupational etiology has been well discussed in atopic diseases such as ARC and bronchial asthma. In this scenario, the patient is exposed to aeroallergens exclusively in the work environment. We reported the etiology to be occupational in 4 patients with AA-EoE [22-24]. The aeroallergen responsible was a protein from wheat flour in 3 cases and α -livetin in the fourth case (Table 1). These 4 patients had type 2 inflammation with IgE-mediated allergy affecting the eyes, nose, and bronchi and a non-IgE-mediated allergy affecting the esophagus. The

triggering allergen in each patient was the same. In 2 cases, the allergen only produced EoE when inhaled and not when eating the food containing the EoE trigger protein (heat-sensitive aeroallergen?). In the other 2 patients, EoE was triggered both by inhalation and by ingestion of the aeroallergen (heat-resistant?).

The above findings are reminiscent of a classic phrase in Allergology, "systemic manifestations of allergic disease", although now it would be more correct to refer to, "systemic manifestations of type 2 inflammation".

4.2 Other Factors Involved

EoE is a complex genetic disease with multiple loci increasing disease risk through environmental risk-modifying factors [57].

As with other atopic diseases, the lack of early exposure to microbial pathogens leads to a defect in immune tolerance and reprograms the commensal intestinal microflora towards a type 2 helper T (T_H2) phenotype. The esophageal microbiota, a rich environment consisting of various bacterial species, is significantly altered by eosinophilic inflammation. Although multiple factors that limit the microbiome in early life have been associated with the development of EoE, the etiology is not fully known [58].

EoE occurs in genetically predisposed individuals. GERD, food allergy, and alterations of the epithelial barrier and possibly of the microbiota combine to allow food allergens or aeroallergens to penetrate the epithelium and activate receptors and inflammatory cells, including eosinophils. The latter secrete toxic granules and cytokines, inducing chronic inflammation, tissue damage, and fibrosis [59,60].

4.3 Etiological Classification

Like other authors [61], we think that the lack of an adequate response to elimination diets in some EoE patients implies a role for antigens other than food allergens. Reviewing the literature, we find emerging evidence on aeroallergens as triggers of EoE. For this reason, we considered it interesting to draw up a potential etiological classification describing the possible causes of the disease reported to date (Figure 1).

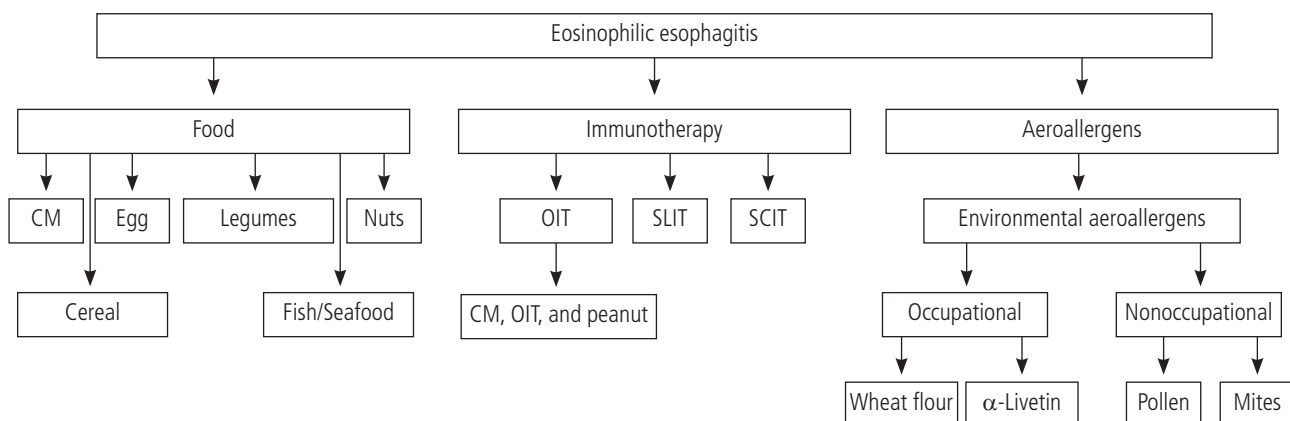


Figure 1. Triggers of eosinophilic esophagitis. CM indicates cow's milk; OIT, oral immunotherapy; SLIT, sublingual immunotherapy; SCIT, subcutaneous immunotherapy.

Based on the existing evidence, EoE can be reactivated by a food allergen or aeroallergen exclusively or by both together. In addition, symptoms and histology findings may be exacerbated by exposure to an allergen other than the first to which the patient is sensitized owing to cross-reactivity between them, since they can share allergenic proteins. In EoE, the clinician must recognize sensitization patterns and cross-reactivity in order to be able to counsel patients on foods and the environment with the aim of ensuring that foods are not unnecessarily restricted from the diet [62,63].

5. Pathophysiology

It is not yet known whether antigens drive accumulation of esophageal eosinophils from the outside-in via the lumen, from the inside-out via systemic immune signals, or both [31]. One study reports the penetration of dust mite antigen into the esophageal epithelium of adults with EoE. However, epithelial staining did not reveal *Dermatophagoides farinae* protein in the controls [64]. The same authors previously reported local accumulation of gluten in the esophagus of patients with EoE [65]. The observation of topical antigen deposition suggests the potential for an outside-in local immune activation. Local antigen presence might be a surrogate marker for lost esophageal barrier function, and the presence or absence of esophageal antigen could be used to gauge adherence to prescribed regimens. The epithelial breakdown would allow local antigen presentation by dendritic cells and macrophages [31].

The loss of serine protease inhibitors can promote epithelial barrier dysfunction and eosinophil infiltration [31]. Group 2 innate lymphocytes are chemoattracted and activated by thymic stromal-derived lymphopoietin and IL-33 and can initiate an early response. T cells could respond to specific local antigens in the later immune phase. IL-5 promotes eosinophil accumulation, and IL-9 promotes mast cell accumulation. Adaptive T_H2 and innate lymphoid cells release IL-4 and IL-13 to promote the B-cell class switch to IgE [31].

Preloaded FcεRI receptors on mast cells and basophils cause degranulation in response to local antigens and release preformed cytokines such as transforming growth factor-β1, with ensuing fibrosis. This local immune response may or may not be appropriately gauged by systemic or cutaneous IgE testing [31]. If local deposition of the antigen triggers EoE, then antigen-specific immunomodulatory therapies such as subcutaneous immunotherapy or percutaneous immunotherapy may be helpful in the treatment of this disease [66,67]. Oral immunotherapy with foods [68,69] and aeroallergens is associated with onset of EoE, which could reflect an outside-in immune response in the esophagus.

The penetration of allergenic proteins could be an indicator of barrier dysfunction. While EoE is often considered a non-IgE-mediated, food antigen-driven hypersensitivity reaction [70], the exact mechanism remains unclear. In fact, some authors consider EoE a mixed disorder, although this view is controversial [71].

Emerging evidence supports the association with immunoglobulin patterns in EoE. For instance, IgG4 is increased in tissues affected by EoE [72]. Murine models

of EoE demonstrate the ability of B cell-deficient mice to develop EE [73]. IgE is not elevated in all EoE patients, and when this antibody is increased, it is challenging to ascertain whether it is due to other underlying allergic conditions. Omalizumab, an anti-IgE monoclonal antibody, was not effective in inducing remission of EoE [6]. This finding, along with granular deposits of IgG4, abundant IgG4-containing plasma cells, and serum levels of IgG4 reactive to specific foods, indicates that EoE is IgG4-mediated in adults [74]. Other authors report that sIgG4 to cow's milk proteins are standard, and high titers have been found in children with the disease. sIgG4 levels are an essential feature of the local immune response that triggers EoE [75].

Although much progress has been made in the pathophysiology of EoE, mechanisms remain to be identified and clarified. There may even be differences in whether the triggers are food allergens or aeroallergens.

6. "Occupational" Eosinophilic Esophagitis: A Subphenotype of Potential Aeroallergen-Triggered EoE Phenotype

Clinical and molecular evidence points to different EoE patient phenotypes and endotypes [76]. Both AA-EoE [56] and FA-EoE could be potential EoE phenotypes.

Occupational EoE refers to new-onset EoE induced exclusively by exposure to substances (aeroallergens) in the workplace [22-24].

An occupational etiology must be considered in the context of an allergic process; we can suspect occupational EoE in cases with a suggestive personal history. For example, in the case of a patient diagnosed with occupational allergic respiratory disease, we take a full history [77], with maximum detail on working conditions: space and environment, a recent specific job, hours, rest, vacations, materials used and how they are used, and air-conditioning and ventilation systems.

Occupational EoE is triggered by inhalation of aeroallergens, although if these are present in food, it can also be stated orally. To confirm an occupational origin, the patient should avoid exposure to aeroallergens and not take them orally. Esophagoscopy with sectional biopsies should be performed at 2 months to determine whether the EoE has remitted. Then, the patient can ingest the aeroallergen but would have to continue avoiding exposure. Esophagoscopy with biopsies should be repeated after a further 2 months. If remission persists, EoE is triggered through the respiratory route, and if EoE is reactivated, it is triggered by aeroallergens through both routes (respiratory and oral).

A correct diagnosis requires a high index of suspicion and a temporal relationship between symptoms and work.

An incorrect diagnosis can have critical socioeconomic consequences for the patient. In Spain, Royal Decree 1299/2006, of November 10 (modified on May 4, 2018) sets out the official classification and recognition criteria. The occupational physicians of an occupational health service can serve as consultants and guide us in the medico-legal management of these cases [78].

Occupational EoE must be diagnosed appropriately to avoid complications and remodeling of the esophageal mucosa.

Treatment consists of total cessation of exposure to the causal aeroallergen through separation of the worker from the job, change of area or activity of the patient in the company, or recommendation of a change of profession. In addition, we must insist on environmental control and labor hygiene measures.

A multidisciplinary team must insist on preventive measures for the worker and the job at 3 levels: primary, eliminating the causal aeroallergen through environmental hygiene; secondary, carrying out regular reviews of workers, asking them about symptoms compatible with EoE for the early detection of EoE; and tertiary, through early treatment of the disease once established. Therefore, the patient should be removed from the workplace as soon as possible, and the EoE should not progress from an inflammatory phenotype to a stenotic phenotype. However, since this is not always possible for socioeconomic reasons, it is necessary to try to induce remission of EoE with drugs.

Prognosis will depend on the duration and intensity of the exposure, the duration of the disease, and the appearance of complications and structural abnormalities in the esophagus.

Cessation of exposure should be accompanied by resolution of the disease, although our experience in this approach is limited. Based on esophagoscopy with biopsies, we have shown EoE to be in remission. Occupational asthma sometimes persists despite cessation of exposure to the trigger. After leaving the workplace, patients are reviewed periodically. In bronchial asthma, reviews are performed every 6 months for the first 2 years and then every year thereafter. It is unclear whether these deadlines could be applied when monitoring occupational EoE, and we need more experience in this possible subphenotype of AA-EoE.

7. Is an Allergist Necessary in the Evaluation of Eosinophilic Esophagitis?

The allergy work-up is essential for the management of both EoE and comorbid atopic conditions (bronchial asthma, ARC, AD, and IgE-FA), which affect most patients with EoE [30,79]. Individuals with EoE frequently experience allergic rhinitis symptoms [30] and may experience seasonal exacerbations of their EoE. Therefore, a thorough evaluation of sensitization to aeroallergens and treatment of allergic rhinitis symptoms is recommended. Furthermore, children with EoE frequently have concomitant IgE-FA [80,81], thus necessitating a careful assessment of each patient's "atopic march," especially considering possible FEDs and food reintroduction. Allergists have broad knowledge of botany and zoology and the panallergens of plant and animal origin, as well as their possible cross-reactivities, especially between allergens that belong to the same family [63].

An allergist can be the primary physician for managing EoE in collaboration with an endoscopist. This strategy has advantages since allergists are experienced in managing atopic disorders in patients with EoE. It is also valuable from a practical point of view and in cases where EoE is activated in

response to flares of other atopic diseases. Similarly, allergists can perform patch or skin testing and order serum testing for allergens involved in atopic disorders to aid diagnosis and treatment. Emerging biologic therapies for other allergic diseases, such as bronchial asthma and AD, may benefit control of EoE. For this reason, it is often worthwhile to refer patients for an allergy work-up, even if primary management is by a gastroenterologist.

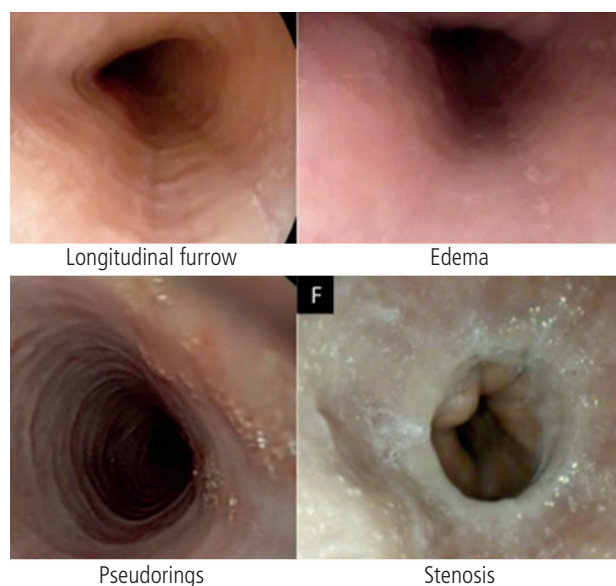


Figure 2. Endoscopic signs of eosinophilic esophagitis: inflammatory phenotype (above) and fibrostenotic phenotype (below).

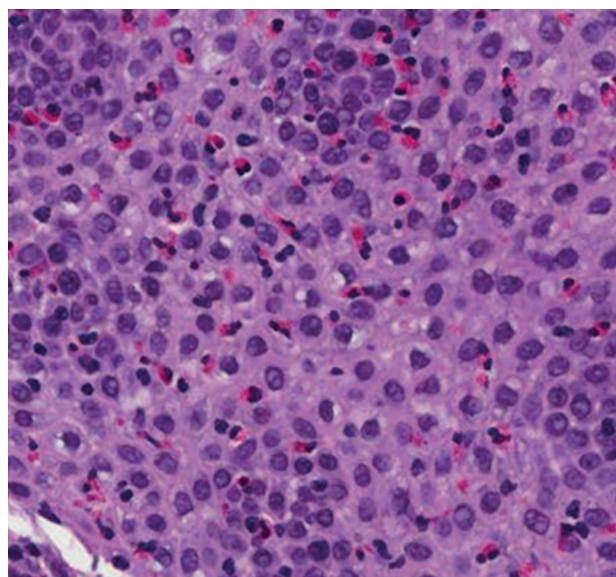


Figure 3. Esophageal epithelium with numerous eosinophils. Hematoxylin-eosin, $\times 20$. Image courtesy of Dr. L. González López, Histopathology Department, Hospital General Universitario de Ciudad Real.

8. Symptoms, Diagnosis, Complications, Natural History, Comorbidities, and Differential Diagnosis

Triggers of EoE (aeroallergens and food) will not influence symptoms, diagnostic procedures (Figures 2 and 3), natural history, complications [82] (Figure 4), comorbidities, or differential diagnosis

9. Treatment

Treatment of AA-EoE is similar to that of other atopic diseases in terms of initial and maintenance therapy [83,84]. The 3 goals of therapy (both in adults and children), namely, resolution of symptoms, control of mucosal inflammation [25], and prevention of short- and long-term complications [85], are aimed at improving patients' quality of life. The choice of treatment depends exclusively on the patient and physician's

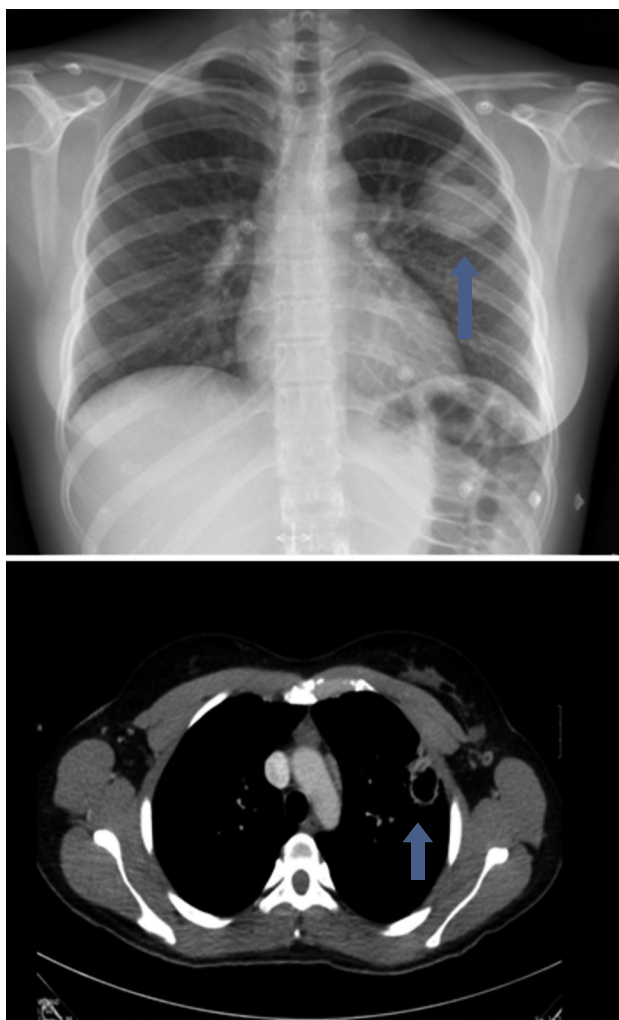


Figure 4. Chest x-ray (upper) and chest computed tomography (below) Pneumonia due to micro-aspirations complicated with a lung abscess secondary to underdiagnosed eosinophilic esophagitis with long-standing classic symptoms.

preference because, no comparative study has shown either of these to be superior to the rest. Therapeutic options include drugs (PPIs and swallowed topical corticosteroids [STC]), FEDs, and esophageal dilation to treat the fibrostenotic phenotype.

Drugs with greater or lesser anti-inflammatory potency gradually reduce esophageal inflammation. PPIs can relieve the symptoms of EoE through acid blockade. Consequently, combinations of therapies are often needed to optimize short- and long-term outcomes [84].

PPIs should be considered in the early stages of treatment, alone or in conjunction with other therapies such as STCs or FEDs [85,86]. Symptoms usually remit in between one-third [87] and half of patients [85]. Controlled clinical trials in adult and pediatric patients with EoE have confirmed that STCs are highly effective in resolving the symptoms and signs of EoE, as reported by Lucendo et al [88] with oral budesonide. PPIs and STCs induce and maintain remission. STCs are more effective, although long-term safety data are insufficient [86].

As for other medical treatments, a small pilot study found that azathioprine and 6-mercaptopurine effectively induced and maintained remission in 3 patients with corticosteroid-refractory EoE. While no biological drug has been approved for EoE [85], there is great hope for dupilumab [88]. Refractoriness, high recurrence rates, and the need for long-term therapies have prompted research into new esophageal-directed formulations of STCs and monoclonal antibodies, some of which are safe in the short term and effective [88].

However, if the causative food can be identified, an elimination diet is an attractive, nonmedical treatment option [25,84] that is favored by allergists.

Several types of FED have been assessed. A meta-analysis demonstrated that a FED is effective in a similar proportion of patients (67.2%) to STC therapy (63.3%). In children, an elemental diet produces nearly complete remission of EoE (90%). However, it is not as effective in adults, where the elemental diet led to remission in 75% of patients [83]. Nevertheless, the many factors against using FEDs for EoE include effect on quality of life and social activities because patients must avoid ubiquitous food antigens such as gluten and milk [85].

In the USA, the 6-food elimination diet (6-FED) eliminates gluten, milk, soy, eggs, nuts, and fish/seafood (crustaceans). Studies in Spain have strongly implicated legumes as a standard antigen [89]. In most studies, milk and cereals were the most frequent causes of EoE [89,90]. The difficulty in implementing this diet has necessitated new strategies. The 4-FED led to remission in 43% of cases. A prospective study of 130 adults and children with EoE found that 6 weeks of a diet that eliminated 2 foods (milk and cereals with gluten), 4 foods (2 foods above plus eggs and legumes), or 6 foods (4 foods above plus nuts and fish/shellfish [crustaceans]) resulted in clinicopathological remission in 43%, 60%, and 79% of patients, respectively. Additionally, compared with the 6-FED, the step-up strategy reduced endoscopic procedures and diagnostic test times by 20% [89].

Allergy testing enables a FED to be established. A recent meta-analysis revealed that this dietary approach led to histologic remission in 45.5% of cases compared with the

72% observed with 6-FED and 90.8% with an elemental diet. A study on FED based on specific IgE to foods ≥ 0.1 kU/L showed clinical-histological remission in 73% of patients, with fewer endoscopies than the 6-FED group [90].

It is essential to agree on treatment of EoE with the patient, family members, or guardians if they are children since this will positively influence adherence. Consequently, a detailed explanation of each of the therapeutic modalities must be provided. We cannot forget that the cause of the EoE must be sought, especially if the patient is interested.

If the EoE has not responded to PPIs and the patient prefers a FED to STCs, it is logical to start with a FED, since foods are the primary triggers. In cases where treatment (dietary and/or pharmacological) proves unsuccessful, it is necessary to consider multiple factors associated with failure, such as lack of adherence to treatment (conscious or unconscious) and hidden allergens, and ultimately ask about profession and hobbies if aeroallergens could be involved.

Currently, endoscopic dilations are reserved for severe untreated fibrostenotic disease that does not respond to medical therapies [86]. Esophageal dilation may be required to increase luminal patency, leading to immediate symptomatic improvement in 95% of patients with EoE who have strictures or narrow-caliber esophagus [91].

Sooner rather than later, several drugs will be approved for the treatment of EoE, especially if they spare corticosteroids in patients with multiple conditions associated with T_H2 inflammation [88]. Personalized therapeutic strategies for the initial and maintenance treatments of EoE should be planned to improve this disease, significantly reduce adverse effects in corticosteroid-dependent patients, and control multiple conditions associated with T_H2 inflammation.

The treatment options mentioned above are valid for AA-EoE. However, in addition, suspected aeroallergens should be avoided for at least 2 months. This approach should be confirmed as helpful for remission of EoE. At this point, the collaboration of the allergist would be necessary since aeroallergens are ubiquitous and the same allergen may have different names. For this reason, recognition of aeroallergens as triggers of EoE can be difficult. Treatment can be complicated because EoE can be triggered by inhaled aeroallergens. Aeroallergens themselves do not trigger EoE when ingested, even though the specific allergen is part of a food. On the other hand, the same aeroallergen has been reported to trigger EoE when it is both ingested in food and inhaled. Treatment can be much more complicated if the causal aeroallergen is in the patient's work environment and the exposure intense (>35 -40 hours per week) (Table 1). Combinations of therapies are often needed to reach optimal short- and long-term results [83].

10. Concluding Remarks

AA-EoE is a potential EoE phenotype that is triggered by inhalation of aeroallergens. However, if the triggering aeroallergen is present in food, it could also behave as a food allergen and trigger oral EoE. Exposure or intake of allergens from the same family with proteins similar to those

of the primary aeroallergen (due to cross-reactivity) could reactivate EoE. Evidence of EoE triggered by aeroallergen immunotherapy is indicated for treating respiratory allergic diseases.

Although many aspects of AA-EoE, such as symptoms, diagnostic procedures, complications, comorbidities, and natural history are like those of FA-EoE, detecting the trigger is crucial if we are to modify the course of the disease. In addition to drugs, it is essential to avoid exposure to causal aeroallergens—environmental and/or occupational—since this should lead to remission of EoE and improve patients' quality of life.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Reed CC, Dellon ES. Eosinophilic Esophagitis. *Med Clin North Am.* 2019;103(1):29-42.
2. Williamson P, Aceves S. Allergies and Eosinophilic Esophagitis—Current Updates for the Pediatric Gastroenterologist. *Curr Gastroenterol Rep.* 2019;20;21(11):56.
3. Nowak-Węgrzyn A, Jarocka-Cyrta E, Moschione Castro A. Food Protein-Induced Enterocolitis Syndrome. *J Invest Allergol Clin Immunol.* 2017;27(1):1-18.
4. Wuthrich B. History of food allergy. *Chem Immunol Allergy.* 2014;100:109-19.
5. Nowak-Węgrzyn A, Katz Y, Mehr SS, Koletzko S. Non-IgE mediated gastrointestinal food allergy. *J Allergy Clin Immunol.* 2015;135:1114-24.
6. Inage E, Furuta GT, Menard-Katcher C, Masterson JC. Eosinophilic esophagitis: pathophysiology and its clinical implications. *Am J Physiol Gastrointest Liver Physiol.* 2018;1;315(5):G879-G886.
7. Curtis C, Ogbogu P. Hypereosinophilic Syndrome. *Clin Rev Allergy Immunol.* 2016;50(2):240-51.
8. Gratacós Gómez AR, González Jimenez OM, Joyanes Romo JB, Palacios Cañas A, Rosa García Rodríguez R, Gomez Torrijos E. Eosinophilic Granulomatosis with Polyangiitis and Atopy: A Case Report. *Explor Res Hypothesis Med.* 2021. DOI: 10.14218 / ERHM.2020.00078 <https://www.xiahepublishing.com/m/2472-0712/ERHM-2020-00078>.
9. Gomez Torrijos E, Gonzalez-Mendiola R, Alvarado M, Avila R, Prieto-Garcia A, Valbuena T, et al. Eosinophilic Esophagitis: Review and Update. *Front Med (Lausanne).* 2018;9:5:247.
10. Attwood SE, Smyrk TC, Demeester TR, Jones JB. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci.* 199;38:109-16.
11. Straumann A, Spichtin HP, Bernoulli R, Loosli J, Vogtlin J. Idiopathic eosinophilic esophagitis: a frequently overlooked disease with distinct clinical aspects and discrete endoscopic findings. *Schweiz Med Wochenschr.* 1994;124:1419-29.

12. 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;109:1503-12.
13. 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;133:1342-63.
14. 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;128:3-20.
15. Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA. ACG Clinical guideline: an evidence-based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol*. 2013;108:679-92.
16. Lucendo AJ, Molina-Infante J, Arias Á, 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 Eur Gastroenterol J*. 2017;5:335-58.
17. Dellon ES, Liacouras CA, Molina-Infante J, Furuta GT, Spergel JM, Zevit N, et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference. *Gastroenterology*. 2018;155(4):1022-33.
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.
19. Arias Á, Lucendo AJ. Epidemiology and risk factors for eosinophilic esophagitis: lessons for clinicians. *Expert Rev Gastroenterol Hepatol*. 2020; 14(11):1069-82.
20. Dellon ES. Epidemiology of eosinophilic esophagitis. *Gastroenterol Clin North Am*. 2014;43(2):201-1.
21. Moawad FJ. Eosinophilic Esophagitis: Incidence and Prevalence. *Gastrointest Endosc Clin N Am*. 2018;28(1):15-25.
22. Gomez-Torrijos E, Rodriguez-Sanchez J, Diaz-Perales A, Garcia R, Feo JF, Garcia C. Occupational allergic multiorgan disease induced by wheat flour. *J Allergy Clin Immunol*. 2015;136(4):1114-6.
23. Gomez Torrijos E, García Rodríguez C, Rodríguez J, De la Roca F, Cárdenas R, Alfara F, et al. Occupational asthma and eosinophilic esophagitis in a patient with egg-bird syndrome. *J Investig Allergol Clin Immunol*. 2015;25(1):61-2.
24. Gómez Torrijos E, Moreno Lozano L, García Rodríguez R. Occupational Allergic Respiratory Disease and Eosinophilic Esophagitis by Wheat Flour in a Baker. *Arch Bronconeumol (Engl Ed)*. 2019;55(10):541-2.
25. Biedermann L, Straumann A, Greuter T, Schreiner P. Eosinophilic esophagitis-established facts, and new horizons. *Semin Immunopathol*. 2021;43(3):319-35.
26. Alexander ES, Martin LJ, Collins MH, Kottyan LC, Sucharew H, He H, et al. Twin and family studies reveal strong environmental and weaker genetic cues explaining heritability of eosinophilic esophagitis. *J Allergy Clin Immunol*. 2014;134:1084-92.
27. Dellon ES, Shaheen O, Koutlas NT, Chang AO, Martin LJ, Rothenberg ME, et al. Early life factors are associated with risk for eosinophilic esophagitis diagnosed in adulthood. *Dis Esophagus*. 2021;34(2): doaa074.
28. Jensen ET, Hoffman K, Shaheen NJ, Genta RM, Dellon ES. Esophageal eosinophilia is increased in rural areas with low population density: results from a national pathology database. *Am J Gastroenterol*. 2014;109:668-75.
29. Hill DA, Grundmeier RW, Ramos M, Spergel JM. Eosinophilic Esophagitis Is a Late Manifestation of the Allergic March. *J Allergy Clin Immunol Pract*. 2018;6(5):1528-33.
30. Castro Jiménez A, Gómez Torrijos E, García Rodríguez R, Feo Brito F, Borja Segade J, Galindo Bonilla PA, et al. Demographic, clinical and allergological characteristics of Eosinophilic Esophagitis in a Spanish central region. *Allergol Immunopathol (Madr)*. 2014;42(5):407-14.
31. Aceves SS. Local Antigen Deposition in Eosinophilic Esophagitis: Implications for Immune Activation. *Gastroenterology*. 2019;157(1):17-20.
32. Fogg MI, Ruchelli E, Spergel JM. Pollen and eosinophilic esophagitis. *J Allergy Clin Immunol*. 2003;112(4):796-7.
33. 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.
34. Dowling PJ, Neuhaus H, Polk BI. The Role of the Environment in Eosinophilic Esophagitis. *Clin Rev All Immunol*. 2019;57:330-9.
35. Miehleke S, Alpan O, Schröder S, Straumann A. Induction of eosinophilic esophagitis by sublingual pollen immunotherapy. *Case Rep Gastroenterol*. 2013;7(3):363-8.
36. Fujiwara Y, Tanaka F, Sawada A, Nakatani Y, Nagami Y, Taira K, et al. A case series of sublingual immunotherapy-induced eosinophilic esophagitis: stop or spit. *Clin J Gastroenterol*. 2021;14(6):1607-11.
37. Béné J, Ley D, Roboubi R, Gottrand F, Gautier S. Eosinophilic esophagitis after desensitization to dust mites with sublingual immunotherapy. *Ann Allergy Asthma Immunol*. 2016;116(6):583-4.
38. Skrabski F, Pérez-Pallisé ME, Domínguez Estirado A, López Tovar C, Bermejo-Becerro A, Rodríguez Mazariego E, et al. Eosinophilic esophagitis caused by grass pollen sublingual immunotherapy with tolerance to a subcutaneous extract. *J Investig Allergol Clin Immunol*. 2021 Oct 15:0. doi: 10.18176/jiaci.0759. Epub ahead of print. PMID: 34661538.
39. Egan M, Atkins D. What Is the Relationship Between Eosinophilic Esophagitis (EoE) and Aeroallergens? Implications for Allergen Immunotherapy. *Curr Allergy Asthma Rep*. 2018; 16;18(8):43.
40. Spergel JM. An allergist's perspective on the evaluation of Eosinophilic Esophagitis. *Best Pract Res Clin Gastroenterol*. 2015;29(5):771-8.
41. Suryawala K, Palle S, Altaf MA. Epidemiology, Clinical Presentation, and Seasonal Variations in the Diagnosis of Children with Eosinophilic Esophagitis in Oklahoma. *South Med J*. 2020;113(1):37-41.
42. Spergel J, Aceves SS. Allergic components of eosinophilic esophagitis. *J Allergy Clin Immunol*. 2018;142(1):1-8.
43. Onbasi K, Sin AZ, Doganavsargil B, Under GF, Bor S, Sebik F. Eosinophil infiltration of the oesophageal mucosa in patients with pollen allergy during the season. *Clin Exp Allergy*. 2005;35:1423-31.

44. 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.
45. 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.
46. Larsson H, Bergquist H, Bove M. The incidence of esophageal bolus impaction: is there a seasonal variation? *Otolaryngol Heal Neck Surg.* 2011;144:186-90.
47. 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.
48. Almansa C, Krishna M, Buchner AM, Gabriel 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.
49. 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.
50. 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;48:81-5.
51. 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.
52. 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.
53. 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
54. 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.
55. 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.
56. Wolf WA, Jerath MR, Dellon ES. The de-novo onset of eosinophilic esophagitis after large volume allergen exposures. *J Gastrointest Liver Dis.* 2013;22:205-8.
57. Kottyan LC, Parameswaran S, Weirauch MT, Rothenberg ME, Martin LJ. The genetic etiology of eosinophilic esophagitis. *J Allergy Clin Immunol.* 2020;145(1):9-15.
58. O'Shea KM, Aceves SS, Dellon ES, Gupta SK, Spergel JM, Furuta GT, et al. Pathophysiology of Eosinophilic Esophagitis. *Gastroenterology.* 2018;154(2):333-45.
59. Vinit C, Dieme A, Courbage S, Dehaine C, Dufeu CM, Jacquemot S, et al. Eosinophilic esophagitis: Pathophysiology, diagnosis, and management. *Arch Pediatr.* 2019;26(3):182-90.
60. Zhang S, Sicherer S, Berin MC, Agyemang A. Pathophysiology of Non-IgE-Mediated Food Allergy. *Immunotargets Ther.* 2021;29;10:431-46.
61. Atkins D. Aeroallergens in Eosinophilic Esophagitis: Significant Triggers or Noise in the System? *J Pediatr Gastroenterol Nutr.* 2017;64(1):1-2.
62. Kazatsky AM, Wood RA. Classification of Food Allergens and Cross-Reactivity. *Curr Allergy Asthma Rep.* 2016;16(3):22.
63. Werfel T, Asero R, Ballmer-Weber BK, Beyer K, Enrique E, Knulst AC, et al. Position paper of the EAACI: food allergy due to immunological cross-reactions with common inhalant allergens. *Allergy.* 2015;70(9):1079-90.
64. Ravi A, Marietta EV, Geno DM, Alexander JA, Murray JA, Katzka DA. Penetration of the esophageal epithelium by dust mite antigen in patients with Eosinophilic esophagitis. *Gastroenterology* 2019;157:255-6.
65. Marietta EV, Geno DM, Smyrk TC, Alexander JA, Murray JA, Katzka DA, et al. Presence of intraepithelial food antigen in patients with active eosinophilic oesophagitis. *Aliment Pharmacol Ther* 2017;45:427-33.
66. Ramirez RM, Jacobs RL. Eosinophilic esophagitis treated with immunotherapy to dust mites. *J Allergy Clin Immunol.* 2013;132(2):503-4.
67. Iglesia EGA, Commings SP, Dellon ES. Complete remission of eosinophilic esophagitis with multi-aeroallergen subcutaneous immunotherapy: A case report. *J Allergy Clin Immunol Pract.* 2021;9(6):2517-9.
68. García Rodríguez R, Méndez Díaz Y, Moreno Lozano L, Extremera Ortega A, Gómez Torrijos E. Eosinophilic Esophagitis After Egg Oral Immunotherapy in an Adult with Egg-Allergy and Egg-Bird Syndrome. *J Investig Allergol Clin Immunol.* 2017;27(4):266-7.
69. Gómez Torrijos E, Mendez Díaz Y, Moreno Lozano L, Extremera Ortega AM, Borja Segade J, Feo Brito JF, et al. Frequency and Course of Eosinophilic Esophagitis During Oral Immunotherapy for Cow's Milk Allergy in a Series of 57 Children. *J Investig Allergol Clin Immunol.* 2017;27(2):132-3.
70. Wilson JM, McGowan EC. Diagnosis and Management of Eosinophilic Esophagitis. *Immunol Allergy Clin North Am.* 2018;38(1):125-39.
71. Mari A, Tsoukali E, Yaccob A. Eosinophilic Esophagitis in Adults: A Concise Overview of an Evolving Disease. *Korean J Fam Med.* 2020;41(2):75-83.
72. Lim AH, Wong S, Nguyen NQ. Eosinophilic Esophagitis and IgG4: Is There a Relationship? *Dig Dis Sci.* 2021 Dec;66(12):4099-108.
73. Mishra A, Schlotman J, Wang M, Rothenberg ME. Critical role for T cell immunity in experimental eosinophilic esophagitis in mice. *J Leukoc Biol.* 2007 Apr;81(4):916-24.
74. Clayton F, Fang JC, Gleich GJ, Lucendo AJ, Olalla JM, Vinson LA, et al. Eosinophilic esophagitis in adults is associated with IgG4 not mediated by IgE. *Gastroenterology.* 2014;147(3):602-9.
75. Schuyler AJ, Wilson JM, Tripathi A, Commings SP, Ogbogu PU, Kruzewski PG, et al. Specific IgG4 antibodies to cow's milk proteins in pediatric patients with eosinophilic esophagitis. *J Allergy Clin Immunol.* 2018;142(1):139-48.
76. Ruffner MA, Cianferoni A. Phenotypes and endotypes in eosinophilic esophagitis. *Ann Allergy Asthma Immunol.* 2020;124(3):233-9.

77. Cormier M, Lemièrre C. Occupational asthma. *Int J Tuberc Lung Dis.* 2020 Jan 1;24(1):8-21.
78. Macías Mora L, Maestre Naranjo MA, Pérez Pimiento AJ, Oliver López C, Angulo Mota N, Rodríguez De La Pinta ML. ¿Asma profesional o agravada por el trabajo? [Occupational Asthma or Work-exacerbated asthma?]. *Arch Prev Riesgos Labor.* 2019;22(4):176-7.
79. Gonzalez-Cervera J, Arias A, Redondo-Gonzalez O, Cano-Mollinedo MM, Terreehorst I, Lucendo AJ. Asociación entre manifestaciones atópicas y esofagitis eosinofílica: una revisión sistemática y metanálisis. *Ann Allergy Asthma Immunol.* 2017;118 (5):582-90. e582.
80. Hill DA, Dudley JW, Spergel JM. Prevalencia de esofagitis eosinofílica en pacientes pediátricos con alergia alimentaria mediada por IgE. *J Allergy Clin Immunol Pract.* 2017;5(2):369-75.
81. Wilson JM, Li RC, McGowan EC. The Role of Food Allergy in Eosinophilic Esophagitis. *J Asthma Allergy.* 2020;15;13:679-88.
82. Barni S, Arasi S, Mastroianni C, Pecoraro L, Giovannini M, Mori F, et al. Pediatric eosinophilic esophagitis: a review for the clinician. *Ital J Pediatr.* 2021 Nov 22;47(1):230.
83. Gonsalves NP, Aceves SS. Diagnosis and treatment of eosinophilic esophagitis. *J Allergy Clin Immunol.* 2020;145(1):1-7.
84. Straumann A, Katzka DA. Diagnosis and Treatment of Eosinophilic Esophagitis. *Gastroenterology.* 2018;154(2):346-59.
85. Gómez-Aldana A, Jaramillo-Santos M, Delgado A, Jaramillo C, Lúquez-Mindiola A. Eosinophilic esophagitis: Current concepts in diagnosis and treatment. *World J Gastroenterol.* 2019 Aug 28;25(32):4598-613.
86. Rossetti D, Isoldi S, Oliva S. Eosinophilic Esophagitis: Update on Diagnosis and Treatment in Pediatric Patients. *Paediatr Drugs.* 2020;22(4):343-56.
87. Gómez-Torrijos E, García-Rodríguez R, Castro-Jiménez A, Rodríguez-Sánchez J, Méndez Díaz Y, Molina-Infante J. The efficacy of step-down therapy in adult patients with proton pump inhibitor-responsive oesophageal eosinophilia. *Aliment Pharmacol Ther.* 2016 Feb;43(4):534-40.
88. Lucendo AJ. Pharmacological treatments for eosinophilic esophagitis: current options and emerging therapies. *Expert Rev Clin Immunol.* 2020 Jan;16(1):63-77.
89. Molina-Infante J, Arias Á, Alcedo J, García-Romero R, Casabona-Frances S, Prieto-García, et al. Step-up empiric elimination diet for pediatric and adult eosinophilic esophagitis: The 2-4-6 study. *J Allergy Clin Immunol.* 2018 Apr;141(4):1365-72.
90. Rodríguez-Sánchez J, Gómez Torrijos E, López Viedma B, de la Santa Belda E, Martín Dávila F, García Rodríguez C, et al. Efficacy of IgE-targeted vs empiric six-food elimination diets for adult eosinophilic oesophagitis. *Allergy.* 2014;69(7):936-42.
91. Surdea-Blaga T, Popovici E, Fadgyas Stănculete M, Dumitrascu DL, Scarpignato C. Eosinophilic Esophagitis: Diagnosis and Current Management. *J Gastrointest Liver Dis.* 2020 Mar 13;29(1):85-97.

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