# Eosinophilic esophagitis due to aeroallergens: A Systematic Review, update, and our experience

**Short title: Eosinophilic esophagitis due to aeroallergens**

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# Eosinophilic esophagitis due to aeroallergens: A Review and update.


## Summary

Eosinophilic esophagitis is a chronic antigen-mediated esophageal disease characterized by symptoms related to esophageal dysfunction and histologically by Th2 inflammation (at least15 eosinophils/high power field) when other secondary systemic and local causes of esophageal eosinophilia are excluded. Though this disease was initially ascribed to a delayed reaction to food allergens, emerging evidence suggests that aeroallergens may also play roles in his pathogenesis and evolution.

Some studies support seasonal variation in Eosinophilic esophagitis diagnosis and disease exacerbations about the increase in aeroallergens to which patients are sensitized. It is also known that this disease can be generated after an extensive, identifiable aeroallergen exposure and after treatment with specific immunotherapy with food or aeroallergens. Recently, it has been postulated that treatment of allergic rhinoconjunctivitis may improve Eosinophilic esophagitis symptoms, though data is 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. Although 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 in the air and being able to inhale them, can also ingest them as part of the food. It is essential to highlight that we must try to discover the cause of the disease since it is crucial for its 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.






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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 claves**: Esofagitis eosinofílica. Aeroalérgenos. Rinitis. Polen. Asma.

## Methods

A bibliographic search was carried out in the following sources: Medline, PubMed, CINAHL, Embase, and Scopus since Eosinophilic Esophagitis was described (1993) until 12-31-20201 by a general practitioner.

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 non-IgE 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 have been reviewed, of which almost 60% have been published in the last five years.

Manuscripts on randomized controlled trials, systematic reviews, reviews, cohort and case-control studies, observational studies, cross-sectional studies, case reports, and single case reports were selected in order of preference. Prospective studies were also preferred over retrospective ones in our selection. We found a high coincidence of publications on the same aspect and with the same results on eosinophilic esophagitis due to aeroallergens, selecting the most recent and best-designed work.

## 1. Definition and introduction

Eosinophilic esophagitis (EoE) is a pathological-clinical entity defined as a chronic esophageal disease, antigen-mediated food and aeroallergens (AAs)- although the latter, to a much lesser extent-, is characterized clinically by symptoms related to esophageal dysfunction and histologically by an eosinophil-predominant Th2 inflammation. Other secondary systemic and local causes of esophageal eosinophilia are excluded [1,2].

Allergic reactions to foods affecting the gastrointestinal tract (GIT) were reported by Hippocrates, who observed that cow milk (CM) could cause urticaria, diarrhea, vomiting, and failure to thrive in infants and resolved when CM was removed from their diet [3,4]. Nowadays, gastrointestinal tract (GIT) immune reactions to CM proteins that are mediated by T lymphocytes with or without the contribution of specific IgE antibodies



 
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are estimated to account for up to 40% of CM protein allergies in infants and young children [3, 5].

EoE, like Food protein-induced enterocolitis syndrome, is a type of non–IgE-mediated, GIT food allergy. Current evidence indicates that cell-mediated responses are essential in both diseases, whereas IgE antibodies to the triggering allergens have minimal implications [3,6]. Diagnosis of EoE relies on clinical, histologic findings and exclusion of causes that show increased eosinophils in GIT and systemic as parasitic intestinal infections, inflammatory bowel disease, celiac disease, achalasia, hypereosinophilic syndrome [7], eosinophilic granulomatosis with polyangiitis [8], etc.

## 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 one 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 guide of EoE was published in 2007 [13] and updated in 2011 [14]. Between both consensuses, the presence of GERD had to be ruled out to make the diagnosis of EoE. In 2011 it was no longer necessary since the EoE and GERD were not mutually exclusive, and both entities could coexist in the same individual. In addition, the existence of esophageal eosinophilia (EE) responsive to proton pump inhibitors drugs (PPIs) drugs was recognized [13,14].

The American College of Gastroenterology 2013 and the European and American Societies of Pediatric Gastroenterology [15] 2014 published their guides for the management of EoE. Finally, the European Guide on EoE has also edited some evidence-based statements and recommendations for diagnosing and treating children and adults [16]. In 2018 they were written Updated International Consensus Diagnostic Criteria Proceedings of the AGREE Conference [17]. In the beginning, EoE was recognized as a form of food allergy. In 2001, from studies carried out in murine models by a group of researchers, we knew it could also be triggered by AAs [18].

## 3. Epidemiology

The rapid expansion of the epidemiology of EoE is being reported, along with cumulative research assessing environmental exposures associated with this 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 recognition and endoscopy volume. Still, the reasons for this evolving epidemiology are not yet fully delineated [20]. Incidence rates for EoE of 5-10 new cases per 100,000 inhabitants/year; EoE now affects more than 1 out of 1,000 people [19]. Other authors reported similar incidence rates, but the prevalence is between 10 and 57 cases/per 100,000 persons [21]. We have not found anything published on the epidemiology of aeroallergen-triggered EoE (AAs-EoE).

 
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Our personal experience is that, from a registry of 386 patients diagnosed with EoE (2012-2021), AAs-EoE has been confirmed in 5 cases, 3 of them by occupational AAs (oAAs-EoE) [22-24] (Table 1). The other two are not published, one is, EoE triggered by oAAs-EoE (Table 1), and the other is sublingual immunotherapy initiated by EoE by pollens (SLITp-EoE). All patients with oAAs-EoE also suffered occupational allergic respiratory disease (OARD); specifically, they had RC and BA.

So, the general frequency of AAs-EoE in our series of patients with EoE is around 1,3% (5/386), and the frequency of oAAs-EoE is about 1% (4/386).

## 4. Etiopathogenesis

The etiopathogenesis of EoE is multifactorial, mainly involving environmental. It can be triggered by food and AAs to a lesser extent; both incite a delayed hypersensitivity Th2 response [25].

### 4.1 *Environmental Factors.*

There is an important limitation regarding the available evidence on environmental factors' potential role in EoE. The studies have been conducted in circumscribed regions or countries, such as EEUU or Spain, representing only a tiny portion of the world, where EoE is common and does not represent areas with low prevalence [25].

The cases of EoE appear to be high in families; 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 the development in the future [25,27]. In addition, consumer antibiotics in infancy might increase the risk of EoE in adult age [25,28]. It may be considered a late manifestation of atopic march [19,25,29] since patients with EoE have a high rate of atopic comorbidities. In a study, 74% of the patients were sensitized to AAs. In comparison, 91% were pollens, and they had concomitant allergic diseases, including allergic rhinoconjunctivitis (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 still don't know each other well, and triggering antigens (Ags) can be challenging to pinpoint [31]. AAs can be the sole driver of esophageal eosinophilia (EE) in some patients, and it can exacerbate existing EoE in others [32,33].

Despite disease manifestations being initially attributed to a delayed reaction to FA, emerging evidence suggests that modifiable host factors and exposure to AAs may also play a critical role in the pathogenesis of EoE (34).

Regarding AAs, some studies support that [34]:

4.1.1 EoE can appear during aeroallergen sublingual immunotherapy (AAs-SLIT) or AAs subcutaneous immunotherapy (AAS-SCIT). In the literature, case reports linked AAs-SLIT to new-onset EoE [34]. The first association of SLIT and EoE was in an adult with



 
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ARC treated with SLIT (hazelnut, birch, and alder). Symptoms of classic EoE developed within four weeks of initiation of therapy, and 164 eosinophils/ high power field (Eos/HPF) were seen on esophageal biopsy. After four weeks of discontinuing ~~SLIT~~, EoE was remitted. Follow-up at one year showed no signs of the EoE [35]. Later, EoE was reported after SLIT with grass tablets and dust mite, remitting after discontinuation [36,37]. Other case report EoE caused by grass pollen SLIT with tolerance to same pollens with SCIT [38]. These authors review the literature, finding, in addition to the previous 2, another 5 case reports, 4 of them triggered by pollen-SLIT (one of them also develops EoE with SCIT) and the other by latex. Recently, a group of authors has published another series of cases [36]. We have studied a case report of AAs-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 portion of EoE patients suggests that Ags other than food allergens (FA) may be involved [18, 39, 40]. There are studies both for and against regarding seasonality of diagnosis of the EoE, mostly of them correlating with pollen season. However, some do not find 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 AAs such as *Aspergillus fumigatus*, dust mite, or cockroach. The authors suggested that intranasal exposure to AAs leads to topical delivery of the Ags to the esophagus and subsequent development of EoE [18,39,40].

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

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

Akei et al. conclude with the first evidence that percutaneous exposure to allergens potently primes for EoE through a Th2-dependent mechanism [42].

A study observed esophageal eosinophilic infiltration in patients with the respiratory allergy during the symptomatic period. The authors found that 26% of patients with ARC without GERD had EoE when biopsied during active allergy respiratory symptoms. There are increased eosinophils in patients with ARC during pollen season than in normal controls. However, the number was lower than those observed in patients with EoE [39,40, 43].

A NY study demonstrated a seasonal correlation between peak grass pollen levels and peak onset of EoE symptoms, both highest from July–to September. Of the 11 pollen taxa examined at each center, only grass pollen was correlated with EoE [44].

Some researchers detected seasonal variation with winter, a low-allergen outdoor season, having the lowest number of newly diagnosed EoE patients [45]. Other authors who



 
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evaluated esophageal bolus impactions found an increase in cases in the summer and fall [46].

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

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

Prasad et al. noted an increased prevalence of EoE diagnosis in the late summer/fall, which paralleled the increase in endoscopies volume [49].

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

Sorser et al. reviewed all esophageal biopsies performed on patients under 21 years old between 2001 and 2006, and 5.8% were patients with EoE; no seasonal correlation was noted, and an absence of correlation between the onset of symptoms and seasons [50].

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

Lucendo et al. performed a systematic review to determine the relationship between seasonal variation and clinical symptoms (food bolus impaction) and diagnosis of EoE. No statistical differences were noted in either EoE diagnoses or food bolus impaction and seasonal variation [54]. Another author thinks perennial AAs and fungi sensitization may lead to nonresponse to EoE treatment in some patients. Therefore, Additional studies are needed to understand further the effect of AAs on EoE [55].

A single case series of adults demonstrated new-onset EoE following a high load of exposure to AAs, including dust mites, pollen, and fungi. However, allergic sensitization to the triggering Ag was only demonstrated in one patient. In addition, there has been no follow-up of these three patients, so nothing is known about the evolution of the AAs-EoE [56].

Since 2012 our group has tried to reach the diagnosis of EoE triggered by AAs (mites, fungi, epithelia, and pollens). We have had several suspected cases, but only one of them has been confirmed (Table 2). Despite that, we ask all the patients with EoE's when they come in for a check-up if they get worse of the DES during the pollen season.



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

We agree with other authors [34,39] that for the triggering of AAs-EoE and exposure to the AAs, the patients must have allergy rhinitis (AR) to remain caught in nasal secretions and swallow post-nasal drip AAs reach the esophagus.

4.1.3 EoE can occur after significant and identifiable exposure to AAs. Our four patients (Table 1) with oAAs-EoE were exposed to a high concentration of AAs at least 40 hours a week. We have no experience in patients with an onset of symptoms consistent with EoE after a single exposure to a high concentration of AAs.

4.1.4. We agree with the emerging hypothesis that treatment of AR may improve symptoms of EoE, although current data is limited to case reports and small series [34]. On the other hand, it is thought that topical nasal corticosteroids used for the control of AR could be helpful in the management of EoE by reducing nasal secretions and postnasal drip, which will reduce the number of AAs retained in the nose and those that reach the esophagus. There is little data in support or oppose this possibility. Further studies are necessary to determine if nasal sprays drug influence the induction of remission, disease control, or symptom reduction in EoE [34].

We would also add from our experience that AR must be moderate-severe with significant nasal obstruction. Faced with this situation, patients are forced to breathe through their mouths, swallowing part of the air containing AAs. Our patients with AAs-EoE had such severe nasal obstruction that it was also accompanied by intermittent anosmia, and all had a steady nasal voice.

There are atopic diseases such as ARC and BA, in which the occupational etiologic is highly studied. You can also have an occupational etiologic (the patient is exposed to AAs exclusively in their work environment). The etiologic is occupational in our four patients with AAs-EoE (22-24). The AA responsible in three of them is a protein from wheat flour, and in the fourth patient is Alpha-livetin (Table 1). These four patients have T2 inflammation with a mediated Ig E allergy affecting the eyes, nose, and bronchi and a non-Ig E mediated allergy affecting the esophagus. The triggering allergen in each patient is the same. In two cases, the allergen produces EoE only when inhaled and not when eating the food containing the EoE trigger protein (heat-sensitive AA?). In the other two, EoE is triggered both by inhalation and by ingestion of AA (heat resistant?).

The above findings remind me of a classic phrase in Allergology, "Systemic Manifestations of Allergic Disease." Although now, it would be more correct to say, "The systemic manifestations of T2 inflammation".

4.2 Other factors involved

EoE is a complex genetic etiologic disease with multiple genetic loci increasing disease risk in environmental disease 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 T helper type 2 (Th2) phenotype. The esophageal microbiota, a rich



 
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environment consisting of various bacterial species, is significantly altered by eosinophilic inflammation. Although multiple factors that limit the microbiome in early life are associated with the development of EoE, currently, the etiologic is not fully known [58].

EoE occurs in an individual with a genetic predisposition. GERD, FA, and alterations of the epithelial barrier and possibly of the microbiota combine to allow FA or AAs 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 that antigens other than food allergens play a role. Reviewing the literature, we find emerging evidence on AAs as triggers of EoE. For this reason, we have considered it interesting to make a potential etiological classification describing the possible motivations of the disease so far related (Table 3).

Based on the existing evidence, EoE can be reactivated by a FA or AA exclusively or for both, from the point of view of its triggers. In addition to the above, the symptoms and histology may be exacerbated by exposure to another allergen to which the patient is sensitized, other than the first, due to cross-reactivity between them since they can share allergenic proteins. In EoE, the clinician needs to recognize sensitization patterns and cross-reactivity to counsel patients on foods and the environment to avoid and ensure that foods are not unnecessarily restricted from the diet [62,63].

## 5. Pathophysiology

It is not yet known precisely whether Ag drives esophageal eosinophil accumulation from the outside in via the lumen, from the inside out via systemic immune signals, or both [31]. A study reports the penetration of dust mite Ag into the esophageal epithelium of adults with EoE. But none of the controls had detectable epithelial staining for *Dermatophagoides* farinae protein [64]. This group previously reported local gluten accumulation in the EoE esophagus. [65]. The observation of topical Ag deposition suggests the potential for an outside-in local immune activation. Local Ag presence might be a surrogate marker for lost esophageal barrier function, and the presence or absence of esophageal Ag could gauge adherence to prescribed regimens. The epithelial breakdown would allow local Ag 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 start 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 Th2 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 Ag and release preformed cytokines such as transforming growth factor-β1 with

 
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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 Ag can EoE triggering, then Ag-specific immunomodulatory therapies such as SCIT or percutaneous immunotherapy may be helpful in this disease treatment [66,67]. OIT with foods [68,69] and aeroallergens is associated with EoE onset, which could reflect an outside-in immune response in the esophagus.

The penetration of allergenic proteins could reflect barrier dysfunction. Taken together, EoE is often considered a non-IgE mediated food-Ags driven hypersensitivity [70], though the exact mechanism remains unclear. In fact (although it is controversial), some authors consider EoE a mixed disorder [71].

There is emerging evidence that supports the association of immunoglobulin patterns in EoE. For instance, IgG4 is increased in EoE tissues [72]. Mouse 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 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 observed granular deposits of IgG4, abundant IgG4-containing plasma cells, and serum levels of IgG4 reactive to specific foods, indicates that, in adults, EoE is IgG4-associated [74]. Other authors find that sIgG4 to CM proteins are standard and high titer in children with you. sIgG4 levels imply 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 known or clarified. There may even be differences in whether the triggers are FA or AAs.

## 6.“Occupational” Eosinophilic esophagitis: Subphenotype of potential aeroallergen triggered EoE phenotype

Clinical and molecular evidence suggests that different eosinophilic esophagitis patient phenotypes and endotypes exist [76]. AAs- EoE [56], as well as FA-EoE, could be potential EoE phenotypes.

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

An occupational etiologic must be considered in the context of an allergic process; we can suspect an occupational EoE due to a suggestive personal history. For example, for the patient who is diagnosed with OARD, we will carry out a thorough anamnesis [77] on the working conditions detailed to the maximum: space and environment, a recent specific job, hours, rest, vacations, materials used, and how are used, and aeration and ventilation systems.

Occupational EoE is triggered by inhalation of AA, but if this is present in food, it can also be stated orally. To confirm occupational origin, the patient should avoid exposure to AA and not take it orally. Performing esophagoscopy with sectional biopsies at two months and see if the EoE has remitted. Then, he ingested the AA, but I would have to continue avoiding exposure. It is repeating esophagoscopy with biopsies after another two



 
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months. If remission persists, EoE is triggered by the respiratory route, and if EoE is reactivated, it is triggered by AA by both courses (respiratory and oral).

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

An incorrect diagnosis can have critical socioeconomic consequences for the worker. In Spain, Royal Decree 1299/2006, of November 10 (modified on May 4, 2018), establishes its 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].

The diagnosis of occupational EoE is essential to avoid complications and remodeling of the esophageal mucosa.

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

A multidisciplinary team must carry out prevention. It must be done on the worker and the job at three levels: primary, eliminating the causal AA through environmental hygiene. Second, carrying out regular reviews of workers, asking them about symptoms compatible with EoE for the early detection of EoE. 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. Although the latter, many times, it is impossible to carry it out for socioeconomic reasons of the patient. Then it is necessary to try to induce remission of EoE with drugs.

The prognosis will depend on the duration and intensity of the exposure, the time of the disease, and the appearance of complications and structural alterations in the esophagus.

Although our experience is minimal, the cessation of exposure should be accompanied by the end of the disease. Due to the esophagoscopy with biopsies performed on our patients, we have verified that the EoE is in remission. Occupational asthma sometimes persists despite the cessation of exposure to the triggering agent. After leaving the workplace, patients will be reviewed periodically. In bronchial asthma, reviews are performed every six months for the first two years and then every year. Could these deadlines be applied in occupational EoE controls? (Currently, we have no answer. We need to have more experience in this possible sub-phenotype of Aas-EoE.

## 7. Is an allergist necessary in the evaluation of Eosinophilic esophagitis?

The allergy evaluation (AE) is essential for both the management of EoE and that of comorbid atopic conditions (BA, ARC, AD, and IgE-FA), which affect most patients with EoE [30,79]. Individuals with EoE frequently experience AR [30] symptoms and may



 
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have seasonal exacerbations of their EoE. Thus, a thorough evaluation of AAs sensitization and treatment of AR symptoms is recommended. Furthermore, children with EoE frequently have concomitant IgE-FA [80,81], and therefore a careful assessment of each patient's "atopic march," especially considering possible FED and food reintroduction, is essential. They know about botany and zoology, the pan-allergens of plant and animal origin, and 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 associated with patients with EoE. This is valuable from a practical point of view and if activation of EoE occurs 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 for diagnosis and treatment. Emerging biologic therapies for other allergic diseases, such as BA and AD, may benefit EoE control. For this reason, it is often worthwhile to refer patients for allergy evaluation, even if primary management is by a gastroenterologist.

## 8. Symptoms. Diagnosis. Complications. Natural history. Comorbidities and differential diagnosis

Triggers of EoE (AAs and food) will not influence symptoms, diagnostic procedures (Figures 1 and 2), natural history, complications [82] (Figure 3), comorbidities, and differential diagnosis

## 9. Treatment

As in other atopic diseases and contemplating initial and maintenance therapy [83,84]. The primary therapeutic goal is triple (both in adults and children): the resolution of symptoms, control of mucosal inflammation, [25] and to prevent short- and long-term complications [85], to achieve an improvement in the quality of life of patients. The choice of treatment depends exclusively on the preference of the patient and the doctor because no comparative study has shown that either of these is superior to the rest. Therapeutic options: Drugs -PPI and swallowed topical corticosteroids (STC)-, food elimination diets (FED), and esophageal dilation to treat the fibrostenotic phenotype.

Drugs. Drugs with greater or lesser anti-inflammatory potency gradually reduce esophageal inflammation. By the acid blockade, PPIs drugs could relieve the symptoms of EoE. Consequently, combinations of therapies are often needed to reach the best short- and long-term results [84].

PPIs should be considered in the early stages of treatment, only or in conjunction with other therapies such as STC or FED [85,86]. They usually remit between 1/3 [87] and half of the patients [85]. There are controlled clinical trials in adult and pediatric patients with EoE that have confirmed that STCs are highly effective in resolving the symptoms and signs of EoE, as performed by Lucendo et al. with budesonide oral [85]. PPIs and CTS induce and maintain remission. STCs are more effective, but insufficient long-term safety data [86].





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Other medical treatment: A small pilot study found that treatment with azathioprine and 6-mercaptopurine effectively induced and maintained remission in 3 patients with steroid-refractory EoE. There is no biological drug approved for EoE [85], but there is great hope for Dupilumab [88]. Refractoriness, high recurrence rates, and the need for long-term therapies have prompted the investigation of new esophageal-directed formulations of STC 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, non-medical treatment option [25, 84], especially among allergists.

FED. There are several types. 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 (ED) produces nearly complete remission of EoE. However, it is not as effective in adults, where the ED led to remission in more than 90% of subjects [83]. Nevertheless, several factors mitigate against using FED for EoE. These affect the quality of life and social activities because patients must avoid ubiquitous food Ags such as gluten and milk [85].

In the United States, 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 Ag [89]. In most studies, milk and cereals were the most frequent causes of EoE [89,90]. The difficulty of this diet has forced new strategies. The 4-FED led to a remission of 43%. A prospective study that included 130 adults and children with EoE found that six weeks of a diet that eliminated two foods (milk and cereals with gluten), four foods (2 foods above plus eggs and legumes), or six 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 directed a FED. A recent meta-analysis revealed that this dietary approach led to histologic remission of 45.5% compared with the72% observed with 6-FED and 90.8% with ED. A study on FED based on specific IgE to foods value ≥0.1kU/L showed clinical-histological remission in 73% of the patients with fewer endoscopies than the 6-FED group [90].

It is essential to agree on EoE treatment with the patient, family members, or guardians if they are children since it will positively influence adherence. This leads to a detailed explanation of each of the therapeutic modalities. 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 FEDs to CTS treatment, it is logical to start with FED since foods are the primary triggers. Suppose there is no success with the treatment (dietary or/and pharmacological). It is necessary to consider multiple factors associated with failure, such as lack of adherence to treatment (conscious or unconscious), hidden allergens, and ultimately ask about the profession and hobbies if the AAs could be involved.





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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, significantly if they save corticosteroids in patients with multiple pathologies associated with Th2 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 steroid-dependent patients and control multiple pathologies with TH2 inflammation.

In AAs-EoE, the treatment options mentioned above are valid. Still, in addition, suspected AA should be avoided for at least two months and confirm that this measure is helpful for EoE remission. At this point, the collaboration of the allergist would be necessary since the AAs are very ubiquitous and not always with the same nomination.

The recognition of AAs as triggers of EoE can be complex. Treatment can be complicated because EoEs triggered by inhaled AAs have been described. AAs themselves do not trigger EoE when ingested, even though it is the exact allergen that is part of a food. On the other hand, other cases described the same AA triggers EoE both when it is ingested in food and inhaled. The treatment can be much more complicated if the causal AA is in the subject's work environment and the intense exposure during 35- 40 hours/week (Table 1). Combinations of therapies are often needed to reach the best short- and long-term results [83].

## 10. Concluding remarks

AAs-EoE is a potential EoE phenotype that is triggered by AA inhalation. Although if the triggering AA 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 like those of the primary AA (due to cross-reactivity) could reactivate EoE. Evidence of EoE triggered by AA immunotherapy is indicated for treating respiratory allergic diseases.

Although many aspects such as symptoms, diagnostic procedures, complications, comorbidities, and natural history are like EoE-AF, detecting the causal trigger is crucial to modifying the history of the disease. In addition to drugs, it is essential to avoid exposure to causal AAs, either environmental or occupational, since it should lead to remission of EoE and improve patients' quality of life.



## Conflict of interest

All authors declare no conflict of interests. It has not received fees for performing.



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Figure 1. Endoscopic signs of eosinophilic esophagitis: inflammatory phenotype (above) and fibrostenotic phenotype (below)

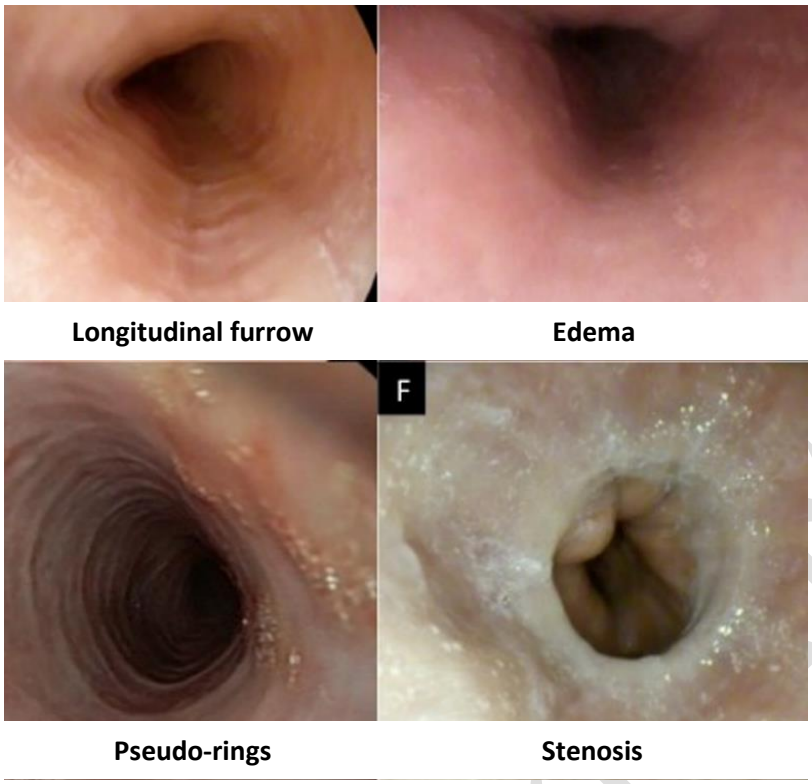


Figure 2. Esophageal epithelium with numerous eosinophils. HE X20.

Image courtesy of Dr. L González López. Pathological A. Service of the HGU.C Real

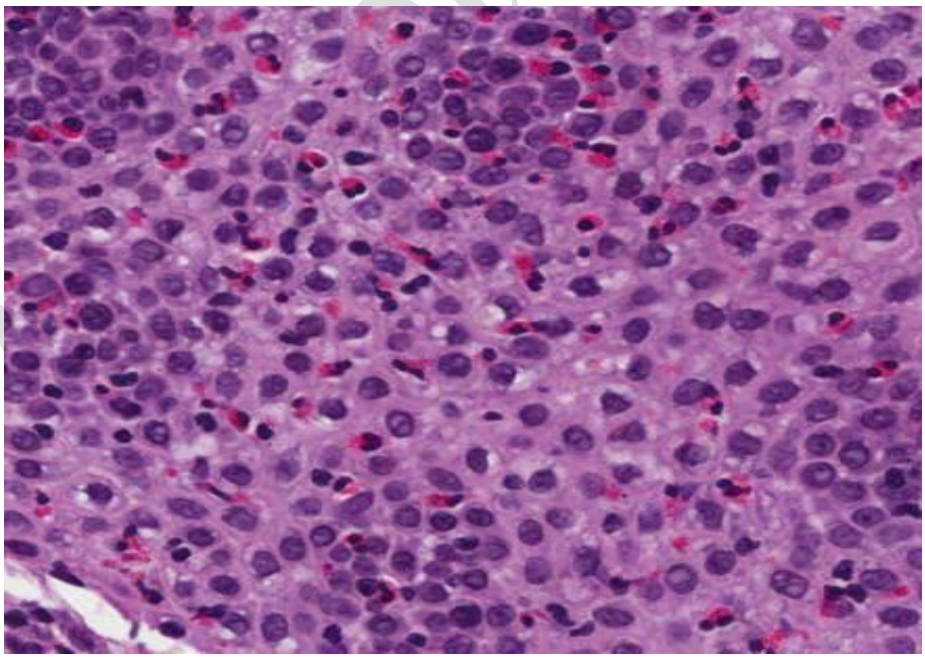

Figure 3. Chest X-ray (upper) and chest computed tomography (below) Pneumonia due to micro-aspirations complicated with a lung abscess secondary to underdiagnosed eosinophilic esophagitis with long-standing classic symptoms.

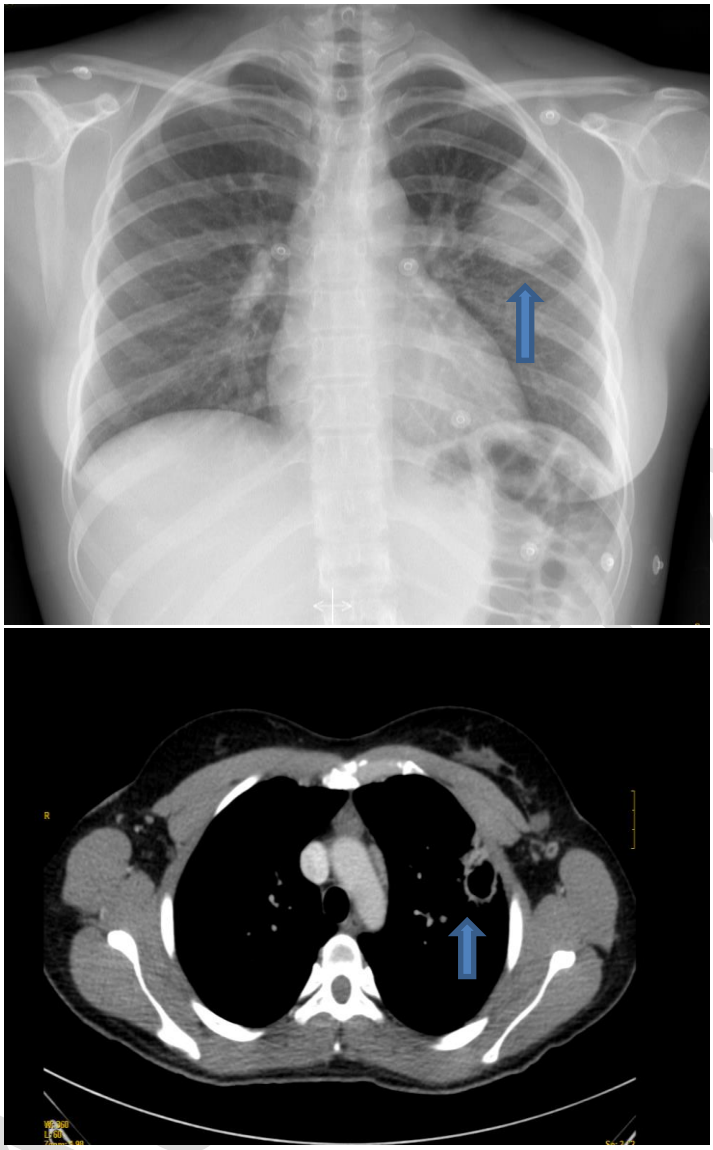

Table 1. Description of patients with eosinophilic esophagitis due to occupational perennial aeroallergens.

| Patients | JACI | JIACI | Arch Broncon | Not published |
|---|---|---|---|---|
| **Age** | 31 | 39 | 49 | 53 |
| **Sex** | Female | Female | Male | Female |
| **Job occupation** | Baker | Nursery school cook | Baker | Churros Factory |
| **o-AA to which you are exposed and responsible for the symptoms** | WF (Gliadin) | Proteins from the yolk, chicken meat, and feathers<br>(Alpha-livetin) | gluten | WF |
| **The latency period between the start of exposure to o-AA and the start of symptoms:**<br>**-Respiratory**<br>**-Digestive** | <br><br>23<br>26 | <br><br>1<br>7 | 30 years<br><br>Simultaneously | <br><br>2 years<br>3 years |
| **Allergy comorbidities** | o- RC &BA to allergy WF | -Egg-Bird Syndrome<br>- o-RS &BA to alpha-livetin protein | o- RC &BA to allergy WF | o- RC &BA to allergy WF |
| **Sensitizations to other allergens of the patient:**<br>**-Aeroallergens**<br>**-Food** | <br><br>Pollens<br>None | Alpha-livetin<br>Doubtful to mites<br>None | <br><br>None<br>None | <br><br>None<br>Anisakis |
| **Digestive symptoms** | Dysphagia, chocking and food impacts | Dysphagia, chocking and food impacts | Dysphagia, chocking and food impacts | Dysphagia |
| **Gastroesophageal reflux disease (GERD)** | No | No | No | At first, it was cataloged as GERD, |

| | | | | |
|---|---|---|---|---|
| | | | | but it was never confirmed |
| **Response to treatment with omeprazole** | No | No | Yes | 20mg/d: No response<br>40 mgs/d: Response during 2 years<br>Later, 80mg/d: No response |
| **Remission EoE** | Yes, after no exposure to heat Flow at work | Yes, at first without eating chicken (Free work).<br>3 months later on, no remissión (She was working) | - | Yes, after no exposure to heat Flow at work |
| **No Exposure to triggering inhaled aeroallergens** | EoE remission | EoE non-remission | EoE non-remission | EoE remission |
| **No Exposure and no intake to triggering aeroallergens** | EoE remission | EoE remission | EoE remission | EoE remission |
| **Evolution** | Asymptomatic, without respiratory or digestive symptoms<br>without exposure to WF | Asymptomatic on vacation and in periods of sick leave, without eating chicken | Asymptomatic, without respiratory and digestive symptoms without exposure to WF, and without eating chicken | Asymptomatic in periods of sick leave and reappearance of symptoms a month after starting work |
| **Esophagoscopy with biopsies after removal of the triggering aeroallergen** | EoE remission | In remission, if the causal allergen is not exposed or ingested | EoE remission | EoE remission one month after cessation of WF exposure and recurrence of symptoms on re-exposure to WF |
| **Current work situation** | None (retired) by occupational disease | Keep working because she is self-employed | None (retired) by occupational disease | Not retired for non-professional problems |
| **Current treatment** | None | STC (400ug/12h) with partial response | None | As she has exposition, perform treatment with STC (400ug/12h) with a total response |

EoE: Eosinophilic esophagitis, WF: Wheat flour, o-AA: Occupational aeroallergen. o-RC&A: Occupational RC and BA, STC: Swallowed topical corticosteroids, TR: Total response, PR: Partial response

Table 2. Cases reported with eosinophilic esophagitis (EoE) were suspected to be triggered by aeroallergens but only confirmed in one of them (EoE triggering by sublingual immunotherapy to pollen)

| | **pAAs-EoE1** | pAAs-EoE2 | pAAs-EoE3 | cAAs-EoE |
|---|---|---|---|---|
| Sex | Woman | Woman | Men | 3 Brothers (Men's) |
| **Age (Year)** | 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** | Pre seasonal sublingual immunotherapy (pollen) | Environmental pollen | Environmental pollen | Cat epithelium |
| **Symptoms without exposure to aeroallergen (2 months)** | Asymptomatic | Dysphagia | Asymptomatic | Dysphagia and choking |
| **No exposure to aeroallergens 2 months** | EoE remission | EoE No remission | EoE remission | EoE NO remission |
| **Reexposure to aeroallergen** | Unrealized | EoE No remission | EoE remission | EoE no remission |
| **Treatment with a food elimination diet** | Unrealized | EoE remission | Unrealized | EoE No remission |
| **Tree 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 |

p-AAs-EoE1: Eosinophilic esophagitis triggered by pollen, p-AAs-EoE2 and 3: Eosinophilic esophagitis not triggered by pollen, p-AAs-EoE4: Eosinophilic esophagitis not triggered by cat epithelium



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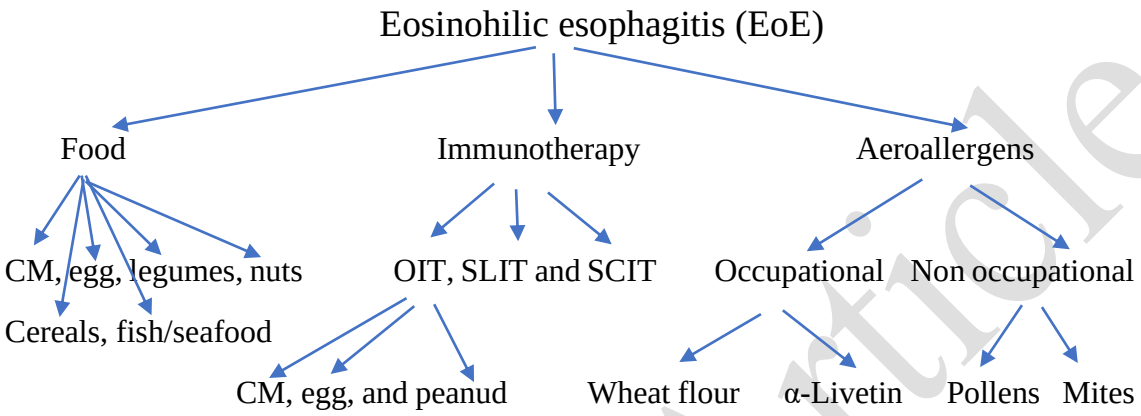
Table 3. Potential etiological classification of EoE




CM: Cow milk, OIT: Oral Immunotherapy, SLIT: Sublingual immunotherapy. SCIT: Subcutaneous immunotherapy