

# Chapter 150

## Treatment for Eosinophilic Esophagitis in adults: where are we?

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### 1 INTRODUCTION

#### Definition

(1) Eosinophilic Esophagitis (EEO) is a disease that falls within a spectrum of eosinophilic gastrointestinal disorders, the inflammation of which has no secondary causes. (2) EEO is defined as a chronic, inflammatory, antigen-mediated esophageal disease, which can be characterized by clinical symptoms related to esophageal dysfunction, (3) such as dysphagia, vomiting, and food impaction (2) and by histology compatible with predominant inflammation of eosinophils. (3) Diagnostic confirmation is confirmed with the presence of 15 or more eosinophils per high-power field in esophageal biopsies performed via upper digestive endoscopy (EDA) and the absence of eosinophilic infiltrate in the other segments of the digestive tract.

#### Epidemiology

(1,4) Although the first case of EEO was described in 1977, it was only in the mid-90s that studies based on evaluations of clinical symptoms and histological changes suggested that it was a distinct condition and not only a manifestation of gastroesophageal reflux disease (GERD).

(5) Since then, both the incidence and prevalence of the disease have been increasing. Although this increase can be attributed to better recognition of the disease and the greater number of esophageal biopsies performed in the same period, (6) studies that analyzed the rates of EDA with biopsy and the changes in the rates of EEO indicate that the increase in incidence modestly outweighs the increase in the rate of

biopsies. Other studies conducted with archived biopsies have also shown the existence of cases of EEO that had gone unnoticed, but at lower rates than the current ones, therefore, the incidence seems to be truly increasing.

(5,7) From a geographical and ethnic point of view, it is believed that EEO occurs mainly in developed countries, mostly in Caucasian men. However, it is necessary to observe that most of the published articles were carried out in these regions.

(8) Practically all studies show that the prevalence of EEO is higher in the masculine sex than in females, both in children and adults. This prevalence is demonstrated in studies from Europe, the USA, and Canada. (9) About two-thirds of the pediatric patients (mean age 8.6 years) with EOS were male. And the proportion increases to 76% among adult patients (mean age 38 years). (8) Thus, the risk for EEO is 2 to 3 times higher for males.

The worldwide incidence of EEO increased after 2008, currently being 7.2 (95% CI 0.8-20.2) in more cases per 100,000 inhabitants-year. Studies conducted in Europe, the U.S., and Canada show that the current incidence rate ranges from 6 to 13 new cases for a population of 100,000 per year. In the pediatric population, it is estimated that the incidence ranges from 0.7 to 10/per 100,000 people per year.

The global prevalence is 28.1 (95% CI 13-49). This estimate is consistent with data from patients of all ages studied in the USA and European countries such as Switzerland, Denmark, and Spain, showing a gradual increase of 40 to 56 cases per 100,000 inhabitants.

Regarding the age group, EEO occurs at different stages of life. However, retrospective studies in pediatric and adult populations have shown that the disease is more common among older children, adolescents, and adults under the age of 50, with peak clinical onset occurring between 30 and 50 years.

Regarding the associated symptoms, the prevalence of eOS in adults with chest pain of noncardiac cause was 6%, from 0.9 to 8% in patients with refractory symptoms of GERD and 7.3% in those with esophageal symptoms and cut compatible with the histological diagnosis of EEO. The prevalence may be even higher in patients with dysphagia and food impaction, 23% and 46%, respectively. In addition, personal history of atopic diseases is documented in 50-60% of cases, and 15-43% of patients also have IgE-mediated food allergies.

In children submitted to EDA by any indication, the combined prevalence of EEO was 3.7% (95% CI 2.4-5.1). Patients under 18 years of age who underwent EDA for abdominal pain had eOS in 6% of cases. 3.7% of children with aerodigestive symptoms were diagnosed with treatment-refractory OSE.

## **Pathophysiology**

**Vision generates about the pathophysiology of EEO:** (10,11) EEO presents multifactorial mechanisms that combine genetic predisposition, environmental factors, and changes in the microbiota and epithelial barrier. The latter seems to play a central role in the pathophysiology of the disease, since it allows

allergens to penetrate the epithelium, activating receptors and inflammatory cells, including eosinophils, initiating the release of alarmins (IL-15, IL-33, and TSLP).

(12) These alarmins, via ILC2s and basophils, initiate a type 2 immune response that is mediated through cytokines (IL-4, IL-5, IL-9, and IL-13). (13) Among the actions of these interleukins, we include the secretion of eotaxin-3, upregulation of periostin in the epithelium and fibroblasts, increased expression of calpain-14, diminution of the expression of filaggrin and desmoglein-1, culminating in the recruitment of eosinophils by chemotaxis, in addition to mast cell recruitment and degranulation.

(12) Concomitantly, dendritic cells present E-related antigens (air and food allergens, for example), which causes the activation of Natural killer (NK) cells and helper 2 (Th2) cells. Both help in the maintenance of cytokine levels, as well as in the orientation of the production of B cells and antibodies (IgE and IgG4).

(10) The immune response to epithelial injury added to the presentation of oEE-related antigens, in general, causes the activation of tissue growth factor TGF-beta. This induces the differentiation of fibroblasts into myofibroblasts, responsible for the synthesis and organization of the extracellular matrix. In addition, this tissue growth factor increases the expression of periostin, which acts both in tissue remodeling and in the recruitment of eosinophils. Thus, TGF-beta plays an important role in the transition from epithelial to mesenchymal tissue (TMS), the development of fibrosis in the lamina propria and submucosa, and dysmotility due to morphological changes in smooth muscle cells.

(10,14) **Genetic factors related to EEO:** Patients with eOS present *upregulation* of the CCL26 gene, responsible for the coding of eotaxin-3, whose function is related to the chemotaxis of eosinophils and basophils. They also have higher expression of the CAPN14 gene, encoding calpain-14, which is an intracellular protease activated by calcium and expressed exclusively in the esophagus, being induced by IL-13. It regulates the DSG1 and FLG genes negatively, decreasing the synthesis of desmoglein-1 and filaggrin, respectively, corroborating the rupture of the epithelial barrier.

An initial study on the genetic influence on EEO identified variations at the 5q22 locus, where the TSLP gene is found, which expresses thymus stromal lymphopoietin (TSLP). It is secreted as a response to epithelial injury, being responsible for the development of Th2 cells, activation of eosinophils, and recruitment of basophils into the esophagus.

STAT6, another EEO-related gene, also induced by IL-13 and IL-4, encodes transcriptional factors that facilitate the expression of these disease-linked genes and is important for the development of Th2 and periostin.

In addition, the C11orf30 gene is related to the higher risk of polysensitization to allergens and encodes EMSY, a gene linked to the LRRC32 protein and responsible for activating STAT6 transcription. Finally, the LRRC31 gene is involved in the production of kallikreins, being an adjunct in the rupture of the epithelial barrier.

(10,13) **Environmental** factors related to EEO: The development of EEO can be instigated by several factors related to the environment, such as food allergens, aeroallergens, breastfeeding deprivation, exposure to antibiotics, cesarean delivery, prematurity, and rural life. On the other hand, it was observed that H. pylori infection can act as a protection against the disease.

**Eosinophils:** (10) The diagnosis of EOS is made by the presence of 15 eosinophils or more in fields of a great increase of esophageal biopsies. Its distribution is varied along the esophagus, requiring the analysis of biopsies from different portions of the tube. (11) In EEO, there is a higher expression of eotaxin-3, which through the GC-protein-coupled CCR3 receptor leads to chemotaxis of these cells. (10) When activated, they undergo degranulation and cytolysis, releasing specialized secondary granules, whose proteins are toxic to the epithelium.

(11,14) The matrix of eosinophil granules is composed of eosinophilic cationic protein (ECP), which increases the permeability of the membrane of target cells, an eosinophil-derived neurotoxin (EDN), which activates dendritic cells and promotes a Th2 cell response, the eosinophilic peroxidase enzyme (EPO) and the major basic protein (MBP), an antagonist of the muscarinic receptor M2, which causes direct cell damage by disrupting the epithelial barrier and activating fibroblasts. (10) In addition, these cells secrete TGF-beta, IL-5, IL-9, IL-13, RANTES, PAF, and LTC4.

(10) **Mast cells:** In EEO, these cells are found in high numbers in the esophagus, due to the upregulation of genes related to their proliferation and the release of IL-5 and IL-9 by eosinophils. Mast cells release TGF-beta, a factor that acts in the remodeling of esophageal tissue, alteration of the functionality of smooth muscle cells, fibrosis in the lamina propria and submucosa, dysmotility, and generation of symptoms.

(15) The implementation of restrictive diets with the elimination of food allergens, administration of corticosteroids, and use of interleukin-5 antibodies results in a decrease in the number of mast cells.

(10) **Basophils:** These cells initiate and maintain, have allergic responses through cytokines, and are considered the main sources of eosinophilic recruitment in EEO through the expression of TSLP.

(10,14) **T cells:** The CD3+, CD4+, and CD8+ types are increased in the esophageal mucosa of the patient with EEO. However, it is the TCD4+ cells that are important in the pathophysiology of this disease. They are activated through the presentation of antigens by dendritic cells, with a Th2 immune response and, consequently, the production of IL-5, IL-13, and hematopoietic prostaglandin-D-synthase (HPGDS).

**NK cells and type 2 lymphocytes:** These lymphocyte lines relate to the Th2 response in EEO. The former produce Th2 cytokines, mainly IL-13, and participates in the process of presenting the cytogenetic. The second, induced by IL-33 and TSLP, expresses CRTH2, which activates the Th2 response.

**TSLP:** This protein can be related to EEO by two pathways. On the one hand, patients with the disease have upregulation of the genes that transcribe and transcribe it to the recipients. On the other hand, its expression is increased by injury of the epithelial barrier, key to the EEO. TSLP induces Th2 immune

response, influences the presentation of antigens through dendritic cells, and acts in the recruitment of basophils to the somus.

**Eotaxin-3:** It is the most abundant cytokine in EEO and has increased expression due to a unique nucleotide polymorphism in its coding gene. It is responsible for the activation and recruitment of eosinophils, which act on fibroblasts, causing fibrosis and dysmotylage.

(10,11) **Interleukin 13:** Its presence is fundamental for the development of several atopic diseases, especially for oS, since it is related to polymorphisms of different genes of this disease. Among its actions in the EEO, we highlight the stimulus for the production of eotaxin-3 by the epithelium, the increase of the chemokine ligand 26 (CCL26), the recruitment of eosinophils from the blood, and the expression of calpain 14 (CAPN14). Esophageal overexpression of IL-13 further blocks the synthesis of desmoglein-1 and filaggrin and increases periostin production by fibroblasts, as well as increasing the survival of T cells.

(10,14) **Interleukin 4:** Like IL-13, IL-4 stimulates the secretion of eotaxin-3 by the epithelium and periostin by fibroblasts. Only IL-4 has specific receptors that induce Th2 differentiation. through IL-4 Th2 activates mast cells, which initially secrete histamine and then prostaglandins and leukotrienes, which will be responsible for controlling inflammatory processes, but without performing the removal of the aggressor targets.

**Interleukin 5:** Acts on the recruitment, proliferation, and activation of eosinophils and mast cells in the esophagus. The absence of this interleucine causes a reduction in eosinophilia and fibrosis, although it does not cause a reduction in the clinical symptoms of oEE.

**Interleukin 9:** It is secreted by eosinophils activated through IL-5 and participates in the proliferation and differentiation of mast cells.

**IgE:** It does not seem to be related to EEO, because of studies involving skin allergic tests, which did not establish a relationship between changes in IgE levels and possible triggers for the disease; animal studies, which despite not having B cells, thus developed the pathology; and studies that demonstrated the non-efficacy of immunoglobulin blockade in the interruption of EEO.

**IgG4:** Patients with eOS have higher expression of IgG4 in esophageal tissue, as well as increased serum levels. And this increase may be related to the extensive tissue remodeling processes associated with eosinophils that usually involve IgG4.

## Clinical picture

(17) Although the disease occurs in all age groups, the symptoms of EEO are distributed differently in pediatric and adult patients. (16, 18) Children in early childhood present with food rejection, dysphagia, abdominal pain, nausea, vomiting and regurgitations, and, less commonly, growth retardation/poor weight evolution. In the case of school-age children, the most frequent symptoms are heartburn, dysphagia, feeding impaction, chest and abdominal pain, and vomiting, in addition to having greater food selectivity. In both

age groups, differential diagnoses should be made in case of fever and weight loss as predominant symptoms.

(16, 18) Adolescents and adults mainly report heartburn and dysphagia for solid foods but also have food impaction, chest pain, and on rare occasions, esophageal perforation (Boerhaave's syndrome). In these age groups, symptoms such as abdominal pain, nausea, vomiting, diarrhea, gastrointestinal bleeding, and weight loss are not common.

(17) Concomitant atopic diseases such as allergic rhinitis/sinusitis, asthma, atopic dermatitis, and food allergy can often be observed in patients with oAe. This question is more enlightening in children since studies have shown a percentage of 50% to 80% of patients with coexisting atopy. In adults, although more scarce, the available studies showed similar results. Importantly, no associated atopic disorder is specific for the diagnosis of OSE.

## Diagnosis

(19) The American College of Gastroenterology has defined guidelines that establish the following diagnostic criteria: 1) Symptoms of esophageal dysfunction; 2) Biopsies of the esophagus, containing predominant eosinophilic inflammation, with 15 eosinophils or more per highly increasing field; 3) Eosinophilia limited to the esophageal go that persists despite treatment with proton pump inhibitors (PPIs); 4) Exclusion of secondary causes of esophageal eosinophilia; and 5) Response to treatment with dietary elimination and topical corticosteroids. The latter criterion helps but is not necessary for diagnosis.

(16, 19) In a recent update, the following criteria were established: 1) Symptoms of esophageal dysfunction; 2) Concomitant atopic conditions; 3) Endoscopic findings of rings, grooves, exudate, stenosis, luminal narrowing, and fragility of the mucosa or crepe paper mucosa; 4) Esophageal biopsy with the presence of 15 or more eosinophils per large magnification field [60 eosinophils/mm<sup>2</sup>]; 5) Eosinophilic infiltration exclusively in the esophagus; and 6) Evaluation of other dystubules that contribute to esophageal eosinophilia.

(16) Like the symptoms, the endoscopic findings of EEo are unevenly distributed among the different age groups. Esophageal rings, strictures, and narrowings are more common in adults. In children, inflammatory findings are predominant such as white plaques or exudates, linear sulci, and edema, in addition to decreased vascularization.

(16, 19) All patients have increased intraepithelial eosinophils that can be found in all regions of the esophagus (eosinophilic infiltrates present in "spots", requiring biopsies of the upper, middle, and lower thirds), but not in other regions of the gastrointestinal tract (GI). Eosinophilic microabscesses and stratifications of eosinophil surfaces are also found.

(16, 17) In addition to eosinophilic changes, histology reveals dilated intercellular spaces (spongiosis), thickened mucosa with hyperplasia of the basal layer (induced by IL-13 and related to

fibrosis), increased number of mast cells and lymphocytes, papillary elongation with extracellular deposition of proteins and granules of eosinophils, and increased collagen deposition in the lamina propria.

(19) When there is clinical suspicion of AOS, even if endoscopy does not present alterations in the esophageal mucosa, a biopsy is necessary.

(16, 19) The following diseases and syndromes stand out as differential diagnoses: Gastroesophageal reflux disease (GERD), infections such as schistosomiasis, anisakiasis and toxocariasis, celiac disease, hypereosinophilic syndrome, inflammatory bowel disease, eosinophilic granulomatosis with polyangiitis, achalasia, Crohn's disease and hypersensitivity to drugs.

## **2 JUSTIFICATION**

Due to the increasing incidence of eosinophilic esophagitis in Brazil and worldwide, the improvement of diagnostic techniques, and the absence of regulation about the treatment for the disease, it is necessary to evaluate the different therapeutic regimens related to EEO for better guidance/aid/guidance of health professionals regarding the clinical management of patients with this pathology.

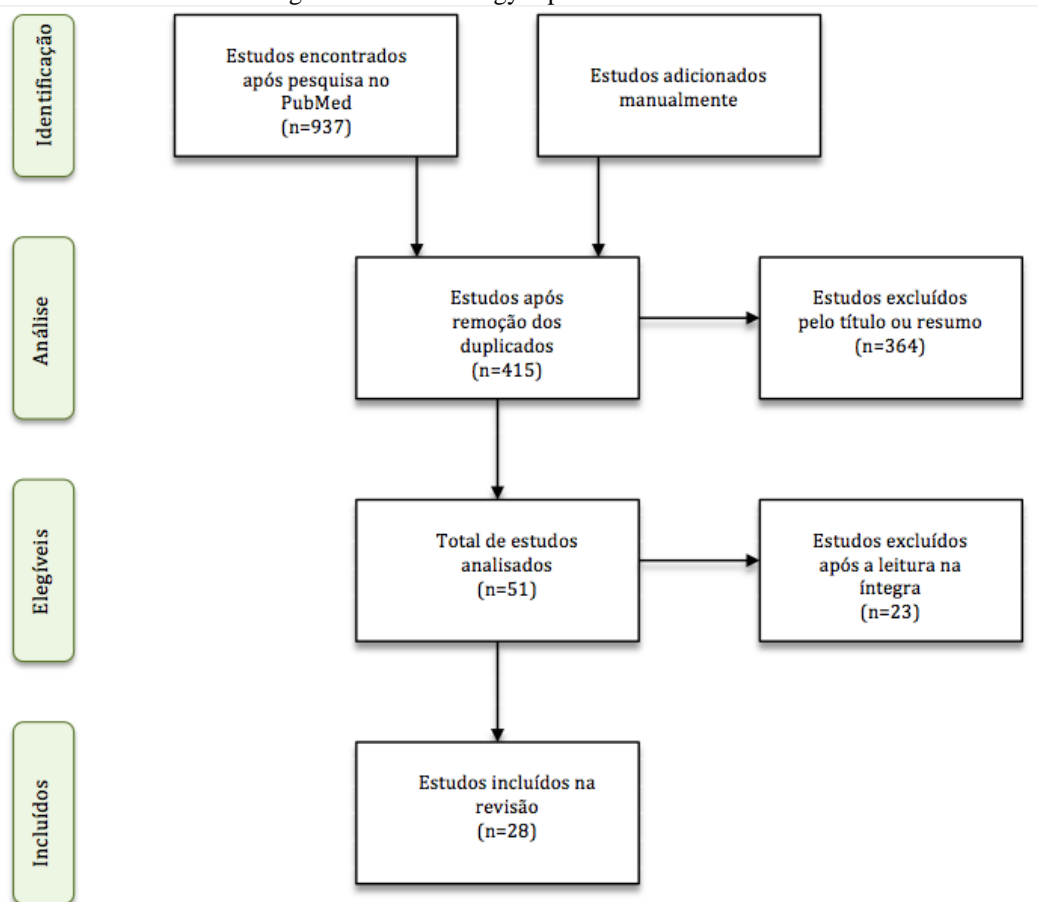
## **3 GOAL**

Analyze the types of treatment for eosinophilic esophagitis and try to define the best therapeutic regimen for this pathology.

## **4 METHODOLOGY**

The platform chosen to carry out this review work was PubMed. Between August 26, 2020, and August 30, 2020, six (6) researchers independently searched for articles with the words "eosinophilic esophagitis" and "treatment", "management", "emerging therapies" or "therapy". A total of 937 articles were selected. The inclusion criteria for study in this review were articles in English that addressed the treatment of EEO in adult patients and were published in the last 5 years. Exclusion criteria were case report articles, research on animals or children, languages other than English, and published before 2015. We then performed the selection of items for the Horizontal Systematic Review by the PRISMA method. After the removal of the 522 duplicate articles, 415 remained, of which 51 remained after reading the title and abstract. With the reading of the articles in full, we removed 23 articles that did not respond exactly to the objective of this review. Finally, this review was followed with 28 articles, these being 3 meta-analyses, 24 systematic reviews, and 1 guideline. The analysis of the articles was initially made by the six (6) authors, but the final choice included senior r. Then, the information collected was arranged in a database shared among the researchers, to differentiate the types of treatment found. Finally, a discussion was made for each type of treatment about the results found, and a conclusion about the best therapeutic scheme for this pathology.

Figure 1. Methodology representation flowchart



## 5 RESULTS AND DISCUSSION

### Diet

The diet is considered one of the pillars in the treatment of eosinophilic esophagitis. To this day, different types of diets have been studied, some more effectively than others. In this work, the following dietary therapies will be addressed: elementary diet; elimination diet directed by allergy tests, and empirical elimination diet. The latter involves the elimination of 6, 4, or 2 foods as well as the progressive elimination of 2-4-6 and 4-6 foods.

#### 1) Elemental diet

An element of dietary therapy consists of an exclusive diet with a hypoallergenic formula based on amino acids. It is sometimes modified by adding one to two solid foods to the diet for better acceptance.

From the analysis of the 28 articles that make up this work, it proved that of the 25 articles that address diet, 23 consider that this method brings results. Therefore, it is concluded that an elemental diet is an approach that is effective in inducing clinical and histological improvements in EEO. Evidence from studies with diet and elementary showed that after a period between 4 and 6 weeks, patients had good clinical and histological remission of the esophagus, with a reduction of eosinophils per field of great increase below 15.



In a meta-analysis conducted in Colombia in 2019 by Andrés Gómez-Aldana et. al 2019, the elemental diet showed patient improvement results of 71% to 90.8%.

In a review study conducted in the United States in 2017, 13 prospective studies showed that the elemental diet has an effectiveness of 90.8% in the histological and clinical remission of 429 patients with oEs.

Despite the proven efficiency of this diet, there are some practical limitations, such as high food prices, unpleasant taste, low adherence to treatment with frequent abandonment, and repercussions on food and social relationships. In addition, the adherence rate of patients is low, due to the high number of endoscopies to confirm allergies, the use of probes, and decreased quality of life of patients due to food restriction.

In general, most of the articles analyzed in this study understand that this type of diet is highly efficient, but that it still presents negative points that should be taken into account during treatment.

## 2) Allergy Test-Directed Elimination Diet

In this type of diet, a skin test of bite and atopy is performed to detect some food that triggers the disease, for its next elimination.

14 articles consider this type of diet ineffective, 4 of average efficacy, and 2 consider it effective. 5 do not discuss the effectiveness of the treatment. The negative point of this type of diet is the inefficiency of skin and serum allergy tests mediated by IgE since EEO has a link between a more dead cause and IgG4.

Added to this is the fact that IgE testing is insufficient to trigger therapy for the disease, as it may not delineate the causative antigen. Because of these factors, remission rates from the use of this strategy are low.

According to AJ Lucendo's 2016 study, the remission rate with this strategy was only 45.5%, with wide heterogeneity in the results.) These results were lower for adults than for children (32.2% vs 47.9%).

This does not despondency between IgE and EEO explains why most articles do not consider treatment of good efficacy. Therefore, this type of diet is not indicated.

## 3) Empirical elimination diet

The empirical elimination diet is a diet in which the most common allergy-causing allergens (food triggers) are eliminated from the diet. A highly positive point is its price about the others. This type of diet, in general, also has negative points: such as the need for endoscopy during the reintroduction of food, which drastically reduces everyday activities, it can be a costly, psychosocial impact, among others.

### Elimination of 6 foods

In the 6-food elimination diet, milk, wheat, egg, soy, nuts, and seafood are eliminated from the patient's diet for about 6 to 8 weeks. These are the 6 foods that the current literature describes as the main causes of inflammation of the esophagus. All the articles that referred to this type of diet considered it effective.

According to the study by Teodora Surdea-Blaga et. al, this approach decreases symptoms and improves the endoscopic and histological features of oEE. In a 2020 guideline, studies demonstrated a 68% histological response rate.

17 articles described as effective, 8 articles did not directly cite, or treated the empirical elimination diet as a whole, without specification.

This proves that the specific withdrawal of these foods drastically reduces eosinophilia from the removal of the origin of inflammation, which are these 6 foods. Among the empirical elimination diets, however, this is the one that has the most restrictions, reducing patient adherence.

### Elimination of 4 foods

In the diet of elimination of 4 foods, leit and, wheat, egg, and legumes are eliminated from the patient's diet. The vast majority of articles consider the elimination treatment of 4 foods to be effective.

12 articles described it as effective, 2 described the treatment as having a medium efficacy, and only 1 considered it with low efficacy. 10 do not directly cite or describe the empirical elimination diet as a whole. The vast majority of articles have designated the elimination treatment of 4 foods as being effective. Efficacy rates were slightly lower relative to the 6-food elimination diet.

In the 2020 guideline, this approach appears to have less effectiveness. Another study showed greater success with this therapy, with 54% of patients achieving the clinical-pathological response.

However, because it is less restrictive, it has a higher adherence of patients, and a higher quality of life during treatment, factors that make it a diet of greater applicability. Therefore, this treatment is effective and applicable.

### Elimination of 2 foods

In the diet of elimination of 2 foods, milk, and wheat are eliminated from the patient's diet.

1 article considered it effective, 1 of average efficacy, and 3 considered it to be ineffective. The rest do not discuss the diet or do not quote it directly.

In this type of diet, the results obtained lead to the conclusion that this is a treatment of low clinical and histological remission since these 2 foods are the origin of eosinophilia and some patients, but not all.

According to Joan W Chen's review article et. al, the two-food elimination diet showed results of 40% efficacy. Another article demonstrates that the elimination of 2 foods led to remission in 43% of patients. Because of this, it is not an advisable treatment because of its low effectiveness.

### Elimination of 2-4-6 foods

This diet was described in 4 articles, of which 3 considered it effective, and only 1 did not consider it effective. The others did not quote it directly or did not discuss its effectiveness. This treatment, in the articles that considered it effective, was the one that obtained the highest rates of clinical and histological remission among the empirical elimination treatments.

The advantage of this treatment is the reduction of the time of diagnosis by 25%, preventing unnecessary diet restriction. In addition, it also reduced the number of endoscopies required during treatment. Such advantages make patients more adherent to treatment, and with better quality of life. Most articles describe it as the most effective empirical elimination therapy.

### Elimination of 2-4 foods

Only cited 2 times, it is considered effective by these articles. Usually, the standard treatment is the elimination of 2-4-6 foods, which explains the lack of articles dealing with this modality of empirical elimination. It follows the same logic as the treatment of 2-4-6 foods, being used to increase patient adherence, due to the better palatability of the diet, and lower psychosocial impacts.

### Elimination of 4-6 foods

One article cites it as effective, and one does not. Usually, the standard treatment is the elimination of 2-4-6 foods, a fact that explains the lack of articles dealing with this modality of empirical elimination. Similar to the treatments of 2-4-6 and 2-4 foods, they increase treatment adherence but do not apply the diet of 2 foods, because it is of low efficacy.

Other 3 articles: One of them presents in general the diet as being the 1st line of treatment, and the others do not present relevant data

Figure 2. Comparative table between diet types

	Elemental diet	Allergy Test-Directed Elimination Diet	6-Food Elimination Diet	4-Food Elimination Diet	2-Food Elimination Diet	Elimination diet of 2-4-6 foods	Elimination diet of 2-4 foods	Elimination diet of 4-6 foods
<b>Positives</b>	Higher rates of histological remission among all treatments (around 90%)	Without so many restrictions	Eliminates the main causes of food allergies; histological improvement rates greater than 60%	Good remission rates; less restrictive	High adhesion about other empirical elimination treatments	Reduction of the diagnostic time by 25%; reduction in the number of endoscopies	Greater palatability; lower psychosocial impacts	Increases patient adherence
<b>Demerits</b>	High price; low palatability; negative repercussion on food	Allergy tests are inefficient at detecting specific food allergies. <b>Not indicated</b>	It has many restrictions, reducing patient adherence	Less effective than the elimination of 6 foods. It has low adhesion as well	Low clinical-histological remission. <b>Not indicated</b>	Many restrictions	Many restrictions	Many restrictions

## Acid suppression

Of the 28 selected articles, 24 of them contain information about acid suppression, while 4 do not mention this therapy.

At first, proton pump inhibitors (PPIs) are pointed out as promising drugs, since 11 articles cite properties of drugs that are related to the pathophysiology of EEO. Among them are mucosal repair, reversal of cytokine transcription, decreased acid production and anti-eosinophilic mechanisms, antioxidants, and anti-fibrotic and anti-inflammatory mechanisms.

However, when clinical and histological remission rates are observed, it is possible to notice a wide variety of results. Of the 28 articles selected, 15 cite rates ranging from 25% to 80% of remission. Among the 15 articles, 12 report remission in less than 72% of cases, while only 3 report results above this percentage. Thus, considering that a remission rate of around 70% to 75% is effective, the use of proton pump inhibitors does not present the desired therapeutic responses.

Similarly, when the clinical remission of histological remission is discriminated, it is possible to infer the low efficacy of this class of drugs. In 7 articles, the clinical remission rate ranges from 60% to 61%, revealing little effectiveness in the symptoms of EEO. In 8 articles, the histological remission rate ranges from 42% to 51%, corroborating the low effectiveness of the class.

Despite the low therapeutic response, 9 articles indicate this therapy as the first line of treatment. This can be explained by the initial use of PPIs in the diagnostic differentiation between EEO and gastroesophageal reflux disease (GERD). Therefore, the patient should use this therapy for 3 months, if symptoms and histology improve, the diagnosis of EEO is ruled out; if there are no improvements, further investigations should be performed. However, the decrease in the production of acid in the stomach and consequent decrease in esophageal aggression cause the symptoms to improve initially in most cases, regardless of the diagnosis, leading doctors to continue with this treatment, without necessarily defining the correct diagnosis or effectively treating the underlying disease.

It is concluded that the use of acid suppression for the treatment of EEO is not the best therapy of choice. The initiation of this treatment may be promising for the differentiation of diagnosis with GERD or in the treatment of patients who concomitantly present both pathologies, but clinical and/or histological remission rates fall far short of those desired. A fact to be highlighted is the ease with which patients and health professionals find access to these drugs (omeprazole does not even require a medical prescription) and the much lower cost of PPIs, when compared to other forms of treatment.

## Steroids

Pharmacological treatment with steroids in remission of EEO is considered the first-line therapeutic method today.

In this review, of the 28 articles analyzed, 26 obtained responses with the use of steroids. Of the articles that had a response to corticosteroids, 92.30% claim that those using topical corticosteroids present

better results in the treatment of oEs. Among the reasons for this better result are speed of action, better contact time of the drug with the wall of the esophagus, efficacy, and lower recurrence after discontinuation of the drugs.

In 18 articles, the efficacy of budesonide and/or fluticasone in the treatment of EEO is specifically mentioned. In two of them, viscous Budesonide showed a tendency to be superior to fluticasone because it stays longer in contact with the mucosa, yet another article also demonstrated that budesonide was more effective for the same reason, but did not specify which type of Budesonide. In addition, a recent study with viscous budesonide demonstrated 100% clinical-histological remission.

Despite the reported efficacy of corticosteroids in the treatment of oEE, four articles show a clinical-histological efficacy of less than 60% (In one, inhalable fluticasone and liquid oral budesonide were used in another swallowed topical corticosteroids, but did not specify which corticosteroid, in another still effervescent tablet of budesonide and oral suspension of budesonide and another swallowed budesonide only).

Recently, a formulation of budesonide orodispersible tablet (BOT), which provided almost 100% efficacy in achieving histological remission after 2 to 6 weeks of therapy, was approved as the first drug to treat eO in adult patients and after being approved by the European Medicines Agency.

Despite the emission of EEO with the use of fluticasone and budesonide, the appearance of esophageal candidiasis was reported as a side effect in 5 articles. Moreover, among the corticosteroids used in the treatment of oEE, methylprednisolone showed clinical improvement and his dramatic logic of the patients with eOS in one of the articles.

One article comments that the ingestion of corticosteroids in the form of viscous liquid is more effective than ingestion by the nebulized and that effervescent bars are also effective as the viscous liquid.

It is worth mentioning that six warn of the side effects of the use of systemic corticosteroids due to the suppression of the adrenal gland and that, therefore, systemic use is reserved for severe and emergency cases.

Of the two articles analyzed that do not present responses to steroid use, one indicates long-term corticosteroid therapy and the other does not report corticosteroid treatment data.

## **Biological**

Biological therapy is a rising pharmacological treatment option that, although showing promise in some respects, has not yet been approved for use in patients with EEO by any regulatory body and is not recommended for therapeutic use by any of the most recent American or European Guidelines.

Among the 28 articles analyzed in this review, 10 classes of biological and immunomodulatory drugs were cited. Dupilumab, a monoclonal antibody that acts by simultaneously blocking IL-4 and IL-13 signaling pathways, has been cited as the most promising, having positive clinical and histological effects

cited in more than one article. The selective antagonist of CRTH2 also seems promising, in the 3 articles where it was cited as effective in clinical and histological remission.

Most of the drugs in clinical trials had varying results. The use of Montelukast, for example, did not present significant results for histological remission, but some articles cited associated clinical improvement. Mepolizumab, anti-IL-5, in turn, caused a reduction in eosinophil infiltration but is not associated with symptom improvement. Immunomodulators such as Azathioprine and 6-mercaptopurine, although they seem effective for patients who had already been treated with steroids, have not been proven effective and one article pointed to adverse effects as a limiting factor of their use. The prostaglandin D2 receptor antagonist was mentioned in 2 articles and despite being clinically and histologically efficient, it had a moderate overall effect.

The drugs anti-IL-13, QAX576, and RPC4046, as well as Omalizumab, anti-IgE, despite causing a decrease in the eosinophil count, did not reach the reduction target of 75%, being considered ineffective. Also not presenting relevant results are the mast cell stabilizer, Sodium Cromoglycate, and the antiTNF-alpha, Infliximab.

### **Dilation and surgery**

The options of treatment with dilation or surgery are considered as the last alternatives in the improvement of the symptoms of eosinophilic esophagitis, besides being, when used, probably in conjunction with other more efficient alternatives.

The key point of dilation is the improvement and relief of symptoms in the long term since it does not interfere in the histological part of the disease, but rather in the structural part, that is, it will not improve the inflammatory part of the disease.

It is important to emphasize that, in the case of dilation, despite the effectiveness in improving symptoms such as impaction and dysphagia, as demonstrated by 20 of the 28 articles analyzed, several maintenance procedures may be necessary, in addition to not discarding the other more conservative therapies.

Surgery is the last alternative, mentioned in only one of the analyzed articles, and is not indicated for symptom relief, only being considered if there are complications in the esophagus, or even rupture. Still, within these articles, 3 of them present limited evidence and do not conclude the effectiveness of dilation, highlighting some obstacles such as the need for maintenance and the lack of improvement of symptoms in some patients with severe esophageal stenosis.

Thus, it can be concluded that the recommendation when the first lines of treatment are not as efficient, is periodic endoscopic dilation in conjunction with diet and medications so that an improvement can be obtained both symptomatically and in the underlying inflammation.

## 6 CONCLUSION

Eosinophilic esophagitis has gained prominence in the last 20 years, due to the increased incidence and diagnostic improvement. It is characterized as a chronic, inflammatory, and immune-mediated esophageal disease, marked by dysphagia, vomiting, food impaction, and the predominant infiltration of eosinophils.

Because it is a relatively new disease, its treatment has not yet been fully defined in the medical literature or regulated by any regulatory agency. Therefore, this review analyzed the most recent perspectives on the treatments available and under study, intending to clarify and guide health professionals regarding the best therapeutic regimen.

The empirical elimination diet should be considered the first treatment option, and the gradual elimination of 2-4-6 foods is the best choice, considering the greater adherence of patients, with less food restriction and the number of reduced endoscopies. Other diet options studied, such as the elimination of 6 foods, although they are equally or even more effective in clinical and histological improvement, find many practical limitations.

In case of non-adaptation or failure of dietary treatment, the main indication is therapy with topical steroids, mainly budesonide, and fluticasone. Less effectively, PPIs may be an option, due to their use for differential diagnosis, low cost, and easy access to the population.

Endoscopic dilatation is associated with other therapeutic options in cases of significant symptoms and a strong impact on quality of life. Although it has clinical effects and a low risk of complications, this method does not alter the underlying inflammation, requiring repeated procedures.

From a future perspective, treatment with biologics seemed promising, but with the tests carried out so far, only Dupilumab has achieved significant results. These drugs are still in the testing phase and require further studies, as none of them is regulated for clinical practice.

Finally, it is important to emphasize that every therapeutic regimen should be individualized for each patient, considering greater adherence to treatment, clinical and histological improvement, and increased quality of life.

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